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AUG 16 2005
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re : U.S. Patent 5,852,195

Issued : December 22, 1998

Inventors : Romines et al.

For : PYRANONE COMPOUNDS USEFUL TO TREAT RETROVIRAL INFECTIONS

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Pharmacia & Upjohn Company LLC, a company organized under the laws of Delaware and formerly known as Pharmacia & Upjohn Company (hereinafter called "the Applicant"), is the assignee and owner of record of U.S. Patent 5,852,195 by virtue of an assignment from each of the individual inventors which was recorded on November 23, 1998 at Reel/Frame 009609/0355. The undersigned registered practitioner, acting on behalf of Pharmacia & Upjohn Company LLC, the owner of record, as its attorney, hereby applies for an extension of the term of U.S. Patent 5,852,195 pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.710 through § 1.791.

SUMMARY OF THE APPLICATION FOR EXTENSION

The Applicant seeks extension of the term of U.S. Patent 5,852,195 for a period of 1278 days, so that expiration date of the patent would be changed from 22 December 2015 to 22 June 2019.

This application for patent term extension is predicated upon the approval of an application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for the drug APTIVUS® capsules, which was approved by the United States Food and Drug Administration on 22 June 2005 (NDA 21-814).

APTIVUS® capsules is a drug product and its sole active ingredient is tipranavir. Thus, tipranavir is a product which has been subject to a regulatory review period before its commercial marketing or use.

Tipranavir has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus Serum-Toxin Act.

The patent for which extension is sought claims tipranavir.

Pursuant to 35 U.S.C. § 156(c)(3), the amount of patent term extension is limited to 1278 days.

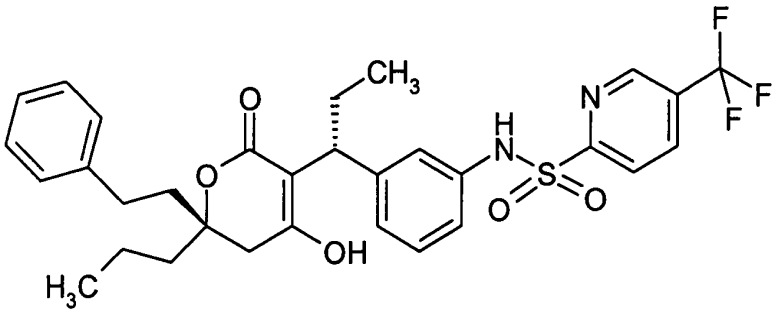
DETAILED DESCRIPTION OF THE BASIS FOR THE APPLICATION

The information given below is that which must be included in this application pursuant to 37 C.F.R. § 1.740(a).

(1) Identification of the Approved Product

The approved product is the compound which is known by the United States Adopted Name (USAN), tipranavir.

Tipranavir has the following structural formula



and is known by the following chemical names:

a) 2-Pyridinesulfonamide, N-[3-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-

(Preferred CA INDEX NAME);

b) 2-Pyridinesulfonamide, N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-, [R-(R*,R*)]-
(Other CA INDEX NAME);

c) 3'-[(1R)-1-[(6R)-5,6-Dihydro-4-hydroxy-2-oxo-6-phenylethyl-6-propyl-2H-pyran-3yl]propyl]-5-(trifluoromethyl)-2-pyridinesulfonanilide
(USP Dictionary of USAN and International Drug Names, 2004 Ed.);

d) (3R,6R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H- pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide; and

e) 5-Trifluoromethyl-N-[3(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6(R)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide.

Tipranavir is also denoted by CAS Registry Number 174484-41-4.

As is evidenced by the text of the labeling (package insert) approved by the U.S. Food and Drug Administration, the approved product, tipranavir, is the active ingredient of APTIVUS® capsules. A copy of the approved labeling is attached hereto as Exhibit A.

(2) Identification of the Federal Statute Under Which Regulatory Review Occurred

The approved product was the subject of regulatory review under the provisions of Section 505 of the Federal Food, Drug & Cosmetic Act, as amended (21 U.S.C. § 355).

(3) Date the Product Received Permission for Commercial Marketing

The product received permission for commercial marketing or use under the provisions of Section 505 of the Federal Food, Drug & Cosmetic Act, as amended

(21 U.S.C. § 355) on 22 June 2005, the date NDA 21-841 was approved by the United States Food and Drug Administration.

(4) Identification of the Active Ingredient in the Drug Product and Statement that It Has Not Been Previously Approved

APTIVUS® capsules is a drug product. Its sole active ingredient is tipranavir. It is the Applicant's belief that tipranavir has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act. The use for which tipranavir has been approved is set forth in the label which was approved by the FDA on June 22, 2005 as follows: APTIVUS® (tipranavir), co-administered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors. The provision of law under which the commercial marketing or use of tipranavir was approved is Section 505 of the Federal Food, Drug & Cosmetic Act, as amended (21 U.S.C. § 355).

(5) Application is Being Submitted Within Sixty Day Period Permitted

This application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f). Such sixty day period will expire on 21 August 2005, but because that date falls on a Sunday, the last day on which the application for patent term extension could be submitted is 22 August 2005, pursuant to 37 C.F.R. § 1.7.

(6) Identification of the Patent for Which Extension is Sought

The patent for which an extension is being sought is U.S. Patent 5,852,195 (hereinafter referred to as the "'195 patent").

The inventors named in the patent are ROMINES, KAREN RENE; BUNDY, GORDON L; SCHWARTZ, THERESA M.; TOMMASI, RUBEN A.; STROHBACH, JOSEPH W.; TURNER, STEVEN, RONALD; THAISRIVONGS, SUVIT; ARISTOFF, PAUL ADRIAN; JOHNSON, PAUL D; SKULNICK, HARVEY IRVING; SKALETZKY, LOUIS L.; ANDERSON, DAVID JOHN; MORRIS, JOEL; GAMMILL, RONALD B.; and LUKE, GEORGE P.

The '195 patent issued on 22 December 1998.

Pursuant to 35 U.S.C. § 154(c), and absent any extension, the term of the '195 patent will expire on 22 December 2015.

(7) Copy of the Patent for Which Extension is Sought

A copy of the '195 patent, including the entire specification (including claims) and drawings is attached hereto as Exhibit B.

(8) Copy of any Disclaimer, Certificate of Correction, Receipt of Maintenance Fee Payment, or Reexamination Certificate Issued in the Patent

No disclaimers have been issued for the '195 patent.

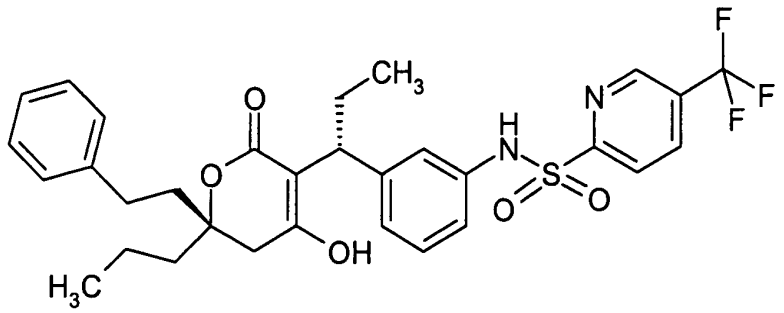
A copy of the certificate of correction issued on 9 October 2001 for the '195 is attached hereto as Exhibit C. No other certificates of correction have been issued.

A copy of a maintenance fee statement showing that the first maintenance fee has been paid is attached hereto as Exhibit D. The second maintenance fee is not yet due.

The '195 patent has not been subjected to reexamination.

(9) Statement that the Patent Claims the Approved Product and Showing that Claims Read on the Approved Product

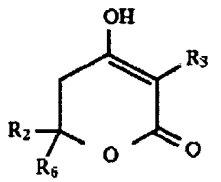
The sole active ingredient of the drug product APTIVUS® capsules is tipranavir. As noted previously, tipranavir has the following structural formula



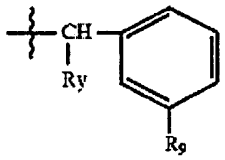
and is known by, inter alia, the chemical name (3R,6R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H- pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide.

The '195 patent contains 5 claims. Claim 1, the sole independent claim, reads as follows:

1. The compound of the formula VI



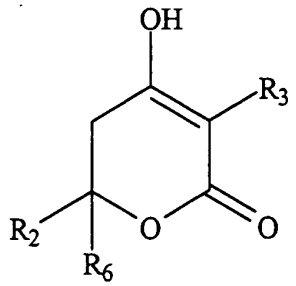
wherein R_2 is
a) $H_3C—CH_2—$, or
b) phenyl-$(CH_2)_2$—;
wherein R_3 is the moiety of formula X



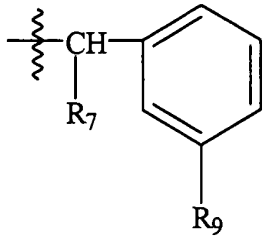
wherein R_6 is
a) $H_3C—(CH_2)_2—$, or
b) phenyl-$(CH_2)_2$—;
wherein R_7 is $H_3C—CH_2—$;
wherein R_9 is $—NHSO_2—$het;
wherein het is 2-pyridinyl substituted at the 5-position by zero (0) or one (1) R_{10};
wherein R_{10} is
a) —CN,
b) $—CF_3$,
c) —NH2, or
d) $—CONH_2$;
or a pharmaceutically acceptable salt thereof.

The certificate of correction dated October 9, 2001, a copy of which is included herewith as Exhibit C, corrects claim 1 by replacing "R_y" with "R_7".

Claim 1 reads on the approved product because tipranavir is the compound of the formula



wherein,
R_2 is phenyl-$(CH_2)_2$-;
R_3 is the moiety of formula



wherein,
R_7 is H_3C-CH_2-,
R_9 is –$NHSO_2$-het,
het is 2-pyridinyl substituted at the 5-position by R_{10}, and
R_{10} is–CF_3; and
wherein R_6 is H_3C-$(CH2)_2$-.

Claim 3 reads on the approved product because the fourth compound of the Markush listing of claim 3 corresponds to the species tiparanvir as well to as all stereoisomers of tipranavir, and because the fifth compound of the Markush listing of claim 3 is the species tipranavir.

Claim 4 reads on the approved product because the first compound of the Markush listing of claim 4 is tipranavir.

(10) <u>Information to Enable Determination of the Regulatory Review Period</u>

The relevant dates and information needed to enable the Secretary of Health and Human Services to determine the applicable regulatory review period appears in Exhibit E, which is attached hereto.

(11) Significant Activities by the Marketing Applicant during the Regulatory Review Period

A description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is provided, on a separate page, by the attached Exhibit F. This exhibit includes four chronologies:

- Agency Contact Reports - Any phone calls, meetings or emails between BI and FDA
- Correspondence from FDA - Faxes or letters (hard copy) from FDA to BI
- IND Log - Listing of all submissions to the tipranavir IND 51,979
- NDA Log - Listing of all amendments to the tipranavir NDA 21-814 (NDA 21-822 (solution) cross references 21-814 for all clinical and non-clinical data)

(12) Statement of Opinion of the Applicant that the Patent is Eligible for Extension Claimed

The attached Exhibit G provides the required statement, on a separate page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

(13) Statement Acknowledging Duty Of Disclosure

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) Payment of Prescribed Fee

The Commissioner is authorized to charge the fee prescribed by 37 C.F.R. § 1.20(j) for receiving and acting upon this application for extension ($1,120.00) to Deposit Account No. 02-2955 (Deposit Account Name: Boehringer Ingelheim Corporation). The Commissioner is authorized to charge any additional fees or underpayments due for consideration of this application, and to credit any overpayments, to this same deposit account.

(15) Correspondence

Correspondence relating to this application for patent term extension should be directed to:

Alan Stempel
Senior Counsel, Intellectual Property
Boehringer Ingelheim Pharmaceuticals, Inc.
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A total of five copies of this application are being submitted, in accordance with MPEP Section 2753.

SUMMATION

Having included in this application all of the requisite information required, the Applicant requests extension of the term of U.S. Patent 5,852,195 for a period of 1278 days.

Respectfully submitted,

Alan Stempel

Alan Stempel

Attorney for the Applicant

Reg. No. 28,991

Date: August 16, 2005

List of Enclosures / Attachments

(1) Return Post Card

(2) Exhibits A-H

EXHIBIT A
COPY OF APPROVED LABELING FOR APTIVUS® CAPSULES

ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from package insert and dispense with product. Dispense the capsules in the unit of use container.

Aptivus®
(tipranavir)
Capsules, 250 mg

Boehringer Ingelheim

Prescribing Information

WARNING

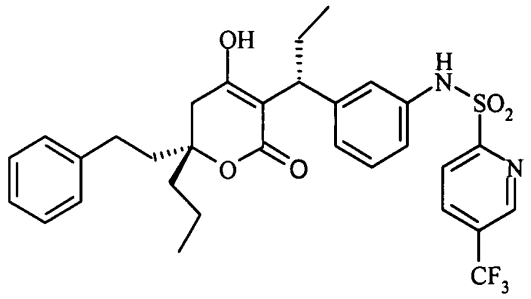
APTIVUS CO-ADMINISTERED WITH 200 MG RITONAVIR HAS BEEN ASSOCIATED WITH REPORTS OF CLINICAL HEPATITIS AND HEPATIC DECOMPENSATION INCLUDING SOME FATALITIES. EXTRA VIGILANCE IS WARRANTED IN PATIENTS WITH CHRONIC HEPATITIS B OR HEPATITIS C CO-INFECTION, AS THESE PATIENTS HAVE AN INCREASED RISK OF HEPATOTOXICITY. (SEE WARNINGS)

DESCRIPTION

APTIVUS® (tipranavir) is the brand name for tipranavir (TPV), a non-peptidic protease inhibitor (PI) of HIV belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides.

APTIVUS soft gelatin capsules are for oral administration. Each capsule contains 250 mg tipranavir. The major inactive ingredients in the capsule are dehydrated alcohol (7% w/w or 0.1 g per capsule), polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.

The chemical name of tipranavir is 2-Pyridinesulfonamide, N-[3-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl). It has a molecular formula of $C_{31}H_{33}F_3N_2O_5S$ and a molecular weight of 602.7. Tipranavir has the following structural formula and is a single stereoisomer with the 1R, 6R configuration.



Tipranavir is a white to off-white to slightly yellow solid. It is freely soluble in dehydrated alcohol and propylene glycol, and insoluble in aqueous buffer at pH 7.5.

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of Action

Tipranavir (TPV) is a non-peptidic HIV-1 protease inhibitor that inhibits the virus-specific processing of the viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

Antiviral Activity

Tipranavir inhibits the replication of laboratory strains of HIV-1 and clinical isolates in acute models of T-cell infection, with 50% effective concentrations (EC_{50}) ranging from 0.03 to 0.07 μM (18-42 ng/mL). Tipranavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M non-clade B isolates (A, C, D, F, G, H, CRF01 AE, CRF02 AG, CRF12 BF). Group O and HIV-2 isolates have reduced susceptibility *in vitro* to tipranavir with EC_{50} values ranging from 0.164 -1 μM and 0.233-0.522 μM, respectively. Protein binding studies have shown that the antiviral activity of tipranavir decreases on average 3.75-fold in conditions where human serum is present. When used with other antiretroviral agents *in vitro*, the combination of tipranavir was additive to antagonistic with other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and generally additive with the NNRTIs (delavirdine, efavirenz, and nevirapine) and the NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine). Tipranavir was synergistic with the HIV fusion inhibitor enfuvirtide. There was no antagonism of the *in vitro* combinations of tipranavir with either adefovir or ribavirin, used in the treatment of viral hepatitis.

Resistance

In vitro: HIV-1 isolates with a decreased susceptibility to tipranavir have been selected *in vitro* and obtained from patients treated with APTIVUS/ritonavir (TPV/ritonavir). HIV-1 isolates that were 87-fold resistant to tipranavir were selected *in vitro* by 9 months and contained 10 protease mutations that developed in the following order: L33F, I84V, K45I, I13V, V32I, V82L, M36I, A71V, L10F, and I54V/T. Changes in the Gag polyprotein CA/P2 cleavage site were also observed following drug selection. Experiments with site-directed mutants of HIV-1 showed that the presence of 6 mutations in the protease coding sequence (I13V, V32I, L33F, K45I, V82L, I84V) conferred > 10-fold reduced susceptibility to tipranavir. Recombinant viruses showing ≥ 3-fold reduced susceptibility to tipranavir were growth impaired.

Clinical Studies of Treatment-Experienced Patients: In Phase 3 studies 1182.12 and 1182.48, multiple protease inhibitor-resistant HIV-1 isolates from 59 highly treatment-experienced patients who received APTIVUS/ritonavir and experienced virologic rebound developed amino acid substitutions that were associated with resistance to tipranavir. The most common amino acid substitutions that developed on 500/200mg APTIVUS/ritonavir in greater than 20% of APTIVUS/ritonavir virologic failure isolates were L33V/I/F, V82T, and I84V. Other substitutions that developed in 10 to 20% of APTIVUS/ritonavir virologic failure isolates included L10V/I/S, I13V, E35D/G/N, I47V, K55R, V82L, and L89V/M. Tipranavir resistance was detected at virologic rebound after an average of

38 weeks of APTIVUS/ritonavir treatment with a median 14-fold decrease in tipranavir susceptibility. The resistance profile in treatment-naïve subjects has not been characterized.

Cross-resistance

Cross-resistance among protease inibitors has been observed. Tipranavir had < 4-fold decreased susceptibility against 90% (94/105) of HIV-1 isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir. Tipranavir-resistant viruses which emerged *in vitro* had decreased susceptibility to the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir and ritonavir but remained sensitive to saquinavir.

Baseline Genotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining tipranavir susceptibility before initiation of APTIVUS/ritonavir therapy. Several analyses were conducted to evaluate the impact of specific mutations and mutational patterns on virologic outcome. Both the type and number of baseline protease inhibitor mutations as well as use of additional active agents (e.g., enfuvirtide) affected APTIVUS/ritonavir response rates in Phase 3 studies 1182.12 and 1182.48 through Week 24 of treatment.

Regression analyses of baseline and/or on-treatment HIV-1 genotypes from 860 highly treatment-experienced patients in Phase 2 and 3 studies demonstrated that mutations at 16 amino acid codons in the HIV protease coding sequence were associated with reduced virologic responses at 24 weeks and/or reduced tipranavir susceptibility: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D or I84V.

Analyses were also conducted to assess virologic outcome by the number of primary protease inhibitor mutations present at baseline. Response rates were reduced if five or more protease inhibitor-associated mutations were present at baseline and subjects did not receive concomitant enfuvirtide with APTIVUS/ritonavir. See Table 1.

Table 1 Phase 3 Studies 1182.12 and 1182.48: Proportion of Responders (confirmed ≥ 1 $\log_{10}$ decrease at Week 24) by Number of Baseline Primary Protease Inhibitor (PI) Mutations

Number of Baseline Primary PI Mutations[a]	APTIVUS/ritonavir N = 513		Comparator PI/ritonavir N = 502	
	No Enfuvirtide	+ Enfuvirtide	No Enfuvirtide	+ Enfuvirtide
Overall	40% (147/368)	64% (93/145)	19% (75/390)	30% (34/112)
1 - 2	68% (26/38)	75% (3/4)	41% (17/41)	100% (2/2)
3 - 4	44% (78/176)	64% (39/61)	23% (39/170)	40% (21/52)
5+	28% (43/151)	64% (51/80)	11% (19/178)	19% (11/57)

[a] Primary PI mutations include any amino acid change at positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 and 90

The median change from baseline in HIV-1 RNA at weeks 2, 4, 8, 16 and 24 was evaluated by the number of baseline primary protease inhibitor mutations (1-4 or ≥ 5) in subjects who received APTIVUS/ritonavir with or without enfuvirtide. The following observations were made:

- Approximately 1.5 $\log_{10}$ decrease in HIV-1 RNA at early time points (Week 2) regardless of the number of baseline primary protease inhibitor mutations (1-4 or 5+).
- Subjects with 5 or more primary protease inhibitor mutations in their HIV-1 at baseline who received APTIVUS/ritonavir without enfuvirtide (n=204) began to lose their antiviral response after Week 4.
- Early HIV-1 RNA decreases (1.5–2 $\log_{10}$) were sustained through Week 24 in subjects with 5 or more primary protease inhibitor mutations at baseline who received enfuvirtide with APTIVUS/ritonavir (n=88).

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

Baseline Phenotype and Virologic Outcome Analyses

APTIVUS/ritonavir response rates were also assessed by baseline tipranavir phenotype. Relationships between baseline phenotypic susceptibility to tipranavir, mutations at protease amino acid codons 33, 82, 84 and 90, tipranavir resistance-associated mutations, and response to APTIVUS/ritonavir therapy at Week 24 are summarized in Table 2. These baseline phenotype groups are not meant to represent clinical susceptibility breakpoints for APTIVUS/ritonavir because the data are based on the select 1182.12 and 1182.48 patient population. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to APTIVUS/ritonavir in highly protease inhibitor-experienced patients.

Table 2 Response by Baseline Tipranavir Phenotype in the 1182.12 and 1182.48 Trials

Baseline Tipranavir Phenotype (Fold Change)[a]	Proportion of Responders[b] with No Enfuvirtide Use	Proportion of Responders[b] with ENF Use	# of Baseline Protease Mutations at 33, 82, 84, 90	# of Baseline Tipranavir Resistance-Associated Mutations[c]	Tipranavir Susceptibility
0-3	45% (74/163)	77% (46/60)	0-2	0-4	Susceptible
> 3-10	21% (10/47)	43% (12/28)	3	5-7	Decreased Susceptibility
> 10	0% (0/8)	57% (4/7)	4	8+	Resistant

[a]Change in tipranavir IC_{50} value from wild-type reference
[b]Confirmed ≥1 $\log_{10}$ decrease at Week 24
[c]Number of amino acid substitutions in HIV protease among L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D or I84V

Pharmacodynamics

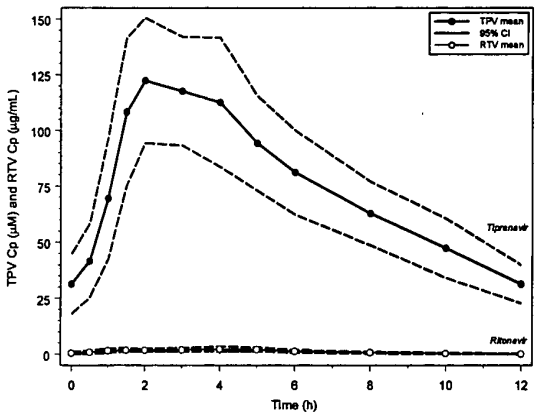
The median Inhibitory Quotient (IQ) determined from 301 highly treatment-experienced patients was about 75 (inter-quartile range: 29-189), from pivotal clinical trials 1182.12 and 1182.48. The IQ is defined as the tipranavir trough concentration divided by the viral IC_{50} value, corrected for protein binding. There was a relationship between the proportion of patients with a $\geq 1 \log_{10}$ reduction of viral load from baseline at week 24 and their IQ value. Among the 206 patients receiving APTIVUS/ritonavir without enfuvirtide, the response rate was 23% in those with an IQ value < 75 and 55% in those with an IQ value ≥ 75. Among the 95 patients receiving APTIVUS/ritonavir with enfuvirtide, the response rates in patients with an IQ value < 75 versus those with an IQ value ≥ 75 were 43% and 84%, respectively. These IQ groups are derived from a select population and are not meant to represent clinical breakpoints.

Pharmacokinetics in Adult Patients

In order to achieve effective tipranavir plasma concentrations and a twice-daily dosing regimen, co-administration of APTIVUS with 200 mg of ritonavir is essential (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Ritonavir inhibits hepatic cytochrome P450 3A (CYP 3A), the intestinal P-glycoprotein (P-gp) efflux pump and possibly intestinal CYP 3A. In a dose-ranging evaluation in 113 HIV-negative male and female volunteers, there was a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations of tipranavir following tipranavir co-administered with low-dose ritonavir (500/200 mg twice daily) compared to tipranavir 500 mg twice daily without ritonavir.

Figure 1 displays mean plasma concentrations of tipranavir and ritonavir at steady state for the 500/200 mg tipranavir/ritonavir dose.

Figure 1 Mean Steady State Tipranavir Plasma Concentrations (95% CI) with Ritonavir Co-administration (tipranavir/ritonavir 500/200 mg BID)



Absorption and Bioavailability

Absorption of tipranavir in humans is limited, although no absolute quantification of absorption is available. Tipranavir is a P-gp substrate, a weak P-gp inhibitor, and appears to be a potent P-gp inducer as well. *In vivo* data suggest that the net effect of tipranavir/ritonavir at the proposed dose regimen (500/200 mg) is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor. Tipranavir trough concentrations at steady-state are about 70% lower than those on Day 1, presumably due to intestinal P-gp induction. Steady state is attained in most subjects after 7-10 days of dosing.

Dosing with APTIVUS 500 mg concomitant with 200 mg ritonavir twice-daily for greater than 2 weeks and without meal restriction produced the following pharmacokinetic parameters for female and male HIV-positive patients. See Table 3.

Table 3 Pharmacokinetic Parameters[a] of tipranavir/ritonavir 500/200 mg for HIV+ Patients by Gender

	Females (n = 14)	Males (n = 106)
$C_{ptrough}$ (μM)	41.6 ± 24.3	35.6 ± 16.7
C_{max} (μM)	94.8 ± 22.8	77.6 ± 16.6
T_{max} (h)	2.9	3.0
AUC_{0-12h} (μM•h)	851 ± 309	710 ± 207
CL (L/h)	1.15	1.27
V (L)	7.7	10.2
$t_{1/2}$ (h)	5.5	6.0

[a]Population pharmacokinetic parameters reported as mean ± standard deviation

Effects of Food on Oral Absorption

APTIVUS capsules co-administered with ritonavir should be taken with food. Bioavailability is increased with a high fat meal. Tipranavir capsules, administered under high fat meal conditions or with a light snack of toast and skimmed milk, were tested in a multiple dose study. High-fat meals (868 kcal, 53% derived from fat, 31% derived from carbohydrates) enhanced the extent of bioavailability (AUC point estimate 1.31, confidence interval 1.23-1.39), but had minimal effect on peak tipranavir concentrations (C_{max} point estimate 1.16, confidence interval 1.09-1.24).

When APTIVUS, co-administered with low-dose ritonavir, was co-administered with 20 mL of aluminum and magnesium-based liquid antacid, tipranavir AUC_{12h}, C_{max} and C_{12h} were reduced by 25-29%. Consideration should be given to separating tipranavir/ritonavir dosing from antacid administration to prevent reduced absorption of tipranavir.

Distribution

Tipranavir is extensively bound to plasma proteins (> 99.9%). It binds to both human serum albumin and α-1-acid glycoprotein. The mean fraction of APTIVUS (dosed without ritonavir) unbound in plasma was similar in clinical samples from healthy volunteers (0.015% ± 0.006%) and HIV-positive patients (0.019% ± 0.076%). Total plasma tipranavir concentrations for these samples ranged from 9 to 82 μM. The unbound fraction of tipranavir appeared to be independent of total drug concentration over this concentration range.

No studies have been conducted to determine the distribution of tipranavir into human cerebrospinal fluid or semen.

Metabolism

In vitro metabolism studies with human liver microsomes indicated that CYP 3A4 is the predominant CYP enzyme involved in tipranavir metabolism.

The oral clearance of tipranavir decreased after the addition of ritonavir, which may represent diminished first-pass clearance of the drug at the gastrointestinal tract as well as the liver.

The metabolism of tipranavir in the presence of 200 mg ritonavir is minimal. Administration of ^{14}C-tipranavir to subjects that received tipranavir/ritonavir 500/200 mg dosed to steady-state demonstrated that unchanged tipranavir accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few metabolites were found in plasma, and all were at trace levels (0.2% or less of the plasma radioactivity). In feces, unchanged tipranavir represented the majority of fecal radioactivity (79.9% of fecal radioactivity). The most abundant fecal metabolite, at 4.9% of fecal radioactivity (3.2% of dose), was a hydroxyl metabolite of tipranavir. In urine, unchanged tipranavir was found in trace amounts (0.5% of urine radioactivity). The most abundant urinary metabolite, at 11.0% of urine radioactivity (0.5% of dose) was a glucuronide conjugate of tipranavir.

Elimination

Administration of ^{14}C-tipranavir to subjects (n=8) that received tipranavir/ritonavir 500/200 mg dosed to steady-state demonstrated that most radioactivity (median 82.3%) was excreted in feces, while only a median of 4.4% of the radioactive dose administered was recovered in urine. In addition, most radioactivity (56%) was excreted between 24 and 96 hours after dosing. The effective mean elimination half-life of tipranavir/ritonavir in healthy volunteers (n=67) and HIV-infected adult patients (n=120) was approximately 4.8 and 6.0 hours, respectively, at steady state following a dose of 500/200 mg twice daily with a light meal.

Pharmacokinetics in Special Populations

Renal Impairment

APTIVUS pharmacokinetics has not been studied in patients with renal dysfunction. However, since the renal clearance of tipranavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Impairment

In a study comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 controls, the single and multiple dose plasma concentrations of tipranavir and ritonavir were increased in patients with hepatic impairment, but were within the range observed in clinical trials. No dosing adjustment is required in patients with mild hepatic impairment.

The influence of moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) on the multiple-dose pharmacokinetics of tipranavir administered with ritonavir has not been evaluated (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**).

Gender

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 studies demonstrated that females generally had higher tipranavir concentrations than males. After 4 weeks of tipranavir/ritonavir 500/200 mg BID, the median plasma trough concentration of tipranavir was 43.9 μM for females and 31.1 μM for males. The difference in concentrations does not warrant a dose adjustment.

Race

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 studies demonstrated that white males generally had more variability in tipranavir concentrations than black males, but the median concentration and the range making up the majority of the data are comparable between the races.

Geriatric Patients

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 studies demonstrated that there was no change in median trough tipranavir concentrations as age increased for either gender through 65 years of age. There were an insufficient number of women greater than age 65 years in the two trials to evaluate the elderly, but the trend of consistent trough tipranavir concentrations with increasing age through 80 years for men was supported.

Pediatric Patients

The pharmacokinetic profile of tipranavir in pediatric patients has not been established.

Drug Interactions

See also **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS, Drug Interactions.**

APTIVUS co-administered with 200 mg of ritonavir can alter plasma exposure of other drugs and other drugs may alter plasma exposure of tipranavir.

Potential for tipranavir/ritonavir to Affect Other Drugs

1. APTIVUS co-administered with 200 mg of ritonavir at the recommended dose, is a net inhibitor of CYP 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP 3A. Thus, co-administration of APTIVUS/ritonavir with drugs highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Co-administration with other CYP 3A substrates may require a dose adjustment or additional monitoring (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

2. Studies in human liver microsomes indicated tipranavir is an inhibitor of CYP 1A2, CYP 2C9, CYP 2C19 and CYP 2D6. The potential net effect of tipranavir/ritonavir on CYP 2D6 is inhibition, because ritonavir is a CYP 2D6 inhibitor. The *in vivo* net effect of tipranavir administered with ritonavir on CYP 1A2, CYP 2C9 and CYP 2C19 is not known. Data are not available to indicate whether tipranavir inhibits or induces glucuronosyl transferases and whether tipranavir induces CYP 1A2, CYP 2C9 and CYP 2C19.

3. Tipranavir is a P-gp substrate, a weak P-gp inhibitor, and appears to be a potent P-gp inducer as well. Data suggest that the net effect of tipranavir co-administered with 200 mg of ritonavir is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor.

4. It is difficult to predict the net effect of APTIVUS administered with ritonavir on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP 3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP 3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.

Potential for Other Drugs to Affect tipranavir

1. Tipranavir is a CYP 3A substrate and a P-gp substrate. Co-administration of APTIVUS/ritonavir and drugs that induce CYP 3A and/or P-gp may decrease tipranavir plasma concentrations. Co-administration of APTIVUS/ritonavir and drugs that inhibit P-gp may increase tipranavir plasma concentrations.

2. Co-administration of APTIVUS/ritonavir with drugs that inhibit CYP 3A may not further increase tipranavir plasma concentrations, because the level of metabolites is low following steady-state administration of APTIVUS/ritonavir 500/200 mg twice daily.

Drug interaction studies were performed with APTIVUS, co-administered with 200 mg of ritonavir, and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of APTIVUS with 200 mg ritonavir, on the AUC, C_{max} and C_{min}, are summarized in Tables 4 and 5. For information regarding clinical recommendations (see **PRECAUTIONS, Drug Interactions, Tables 8** and **9**).

Table 4 Drug Interactions: Pharmacokinetic Parameters for Tipranavir in the Presence of Co-administered Drugs

Co-administered Drug	Co-administered Drug Dose (Schedule)	TPV/ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Tipranavir Pharmacokinetic Parameters with/without Co-administered Drug; No Effect = 1.00		
					C_{max}	AUC	C_{min}
Atorvastatin	10 mg (1 dose)	500/200 mg BID (14 doses)	22	↔	0.96 (0.86, 1.07)	1.08 (1.00, 1.15)	1.04 (0.89, 1.22)
Clarithromycin	500 mg BID (25 doses)	500/200 mg BID*	24(68)	↑	1.40 (1.24, 1.47)	1.66 (1.43, 1.73)	2.00 (1.58, 2.47)
Didanosine	400 mg (1 dose)	500/100 mg BID (27 doses)	5	↓	1.32 (1.09, 1.60)	1.08 (0.82, 1.42)	0.66 (0.31, 1.43)
Efavirenz	600 mg QD (8 doses)	500/100 mg BID*	21(89)	↓	0.79 (0.69, 0.89)	0.69 (0.57 , 0.83)	0.58 (0.36 , 0.86)
		750/200 mg BID*	25(100)	↔	0.97 (0.85,1.09)	1.01 (0.85 , 1.18)	0.97 (0.69 , 1.28)
Ethinyl estradiol /Norethindrone	0.035/1.0 mg (1 dose)	500/100 mg BID (21 doses)	21	↓	1.10 (0.98, 1.24)	0.98 (0.88, 1.11)	0.73 (0.59, 0.90)
		750/200 mg BID (21 doses)	13	↔	1.01 (0.96, 1.06)	0.98 (0.90, 1.07)	0.91 (0.69, 1.20)
Fluconazole	100 mg QD (12 dose)	500/200 mg BID*	20(68)	↑	1.32 (1.18 ,1.47)	1.50 (1.29 , 1.73)	1.69 (1.33, 2.09)
Loperamide	16 mg (1 dose)	750/200 mg BID (21 doses)	24	↓	1.03 (0.92, 1.17)	0.98 (0.86, 1.12)	0.74 (0.62, 0.88)
Rifabutin	150 mg (1 dose)	500/200 mg BID (15 doses)	21	↔	0.99 (0.93, 1.07)	1.00 (0.96, 1.04)	1.16 (1.07, 1.27)
Tenofovir	300 mg (1 dose)	500/100 mg BID	22	↓	0.83 (0.74, 0.94)	0.82 (0.75, 0.91)	0.79 (0.70, 0.90)
		750/200 mg BID (23 doses)	20	↔	0.89 (0.84, 0.96)	0.91 (0.85, 0.97)	0.88 (0.78, 1.00)
Zidovudine	300 mg (1 dose)	500/100 mg BID	29	↓	0.87 (0.80, 0.94)	0.82 (0.76, 0.89)	0.77 (0.68, 0.87)
		750/200 mg BID (23 doses)	25	↔	1.02 (0.94, 1.10)	1.02 (0.92, 1.13)	1.07 (0.86, 1.34)

*steady state comparison to historical data

Table 5 Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of tipranavir/ritonavir

Co-administered Drug	Co-administered Drug Dose (Schedule)	TPV/ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Co-administered Drug Pharmacokinetic Parameters with/without TPV/ritonavir; No Effect = 1.00		
					C_{max}	AUC	C_{min}
Amprenavir/RTV[a]	600/100 mg BID (27 doses)	500/200 mg BID (28 doses)	16	↓	0.61 (0.51, 0.73)[d]	0.56 (0.49, 0.64)[d]	0.45 (0.38, 0.53)[d]
			74	↓	-	-	0.44 (0.39, 0.49)[e]
Abacavir[a]	300 mg BID (43 doses)	250/200 mg BID	28	↓	0.56 (0.48, 0.66)	0.56 (0.49, 0.63)	-
		750/100 mg BID	14	↓	0.54 (0.47, 0.63)	0.64 (0.55, 0.74)	-
		1250/100 mg BID (42 doses)	11	↓	0.48 (0.42, 0.53)	0.65 (0.55, 0.76)	-
Atorvastatin	10 mg (1 dose)	500/200 mg BID (17 doses)	22	↑	8.61 (7.25, 10.21)	9.36 (8.02, 10.94)	5.19 (4.21, 6.40)
Orthohydroxy-atorvastatin			21, 12, 17	↓	0.02 (0.02, 0.03)	0.11 (0.08, 0.17)	0.07 (0.06, 0.08)
Parahydroxy-atorvastatin			13, 22, 1	↓	1.04 (0.87, 1.25)	0.18 (0.14, 0.24)	0.33 (NA)
Clarithromycin	500 mg BID (25 doses)	500/200 mg BID (15 doses)	21	↑	0.95 (0.83, 1.09)	1.19 (1.04, 1.37)	1.68 (1.42, 1.98)
14-OH-clarithromycin			21	↓	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.05 (0.04, 0.07)
Didanosine[b]	200 mg BID, ≥60 kg	250/200 mg BID	10	↓	0.57 (0.42, 0.79)	0.67 (0.51, 0.88)	-
		750/100 mg BID	8	↔	0.76 (0.49, 1.17)	0.97 (0.64, 1.47)	-
	125 mg BID, <60 kg (43 doses)	1250/100 mg BID (42 doses)	9	↔	0.77 (0.47,1.26)	0.87 (0.47, 1.65)	-
	400 mg (1 dose)	500/100 mg BID (27 doses)	5	↔	0.80 (0.63, 1.02)	0.90 (0.72, 1.11)	1.17 (0.62, 2.20)
Efavirenz[b]	600 mg QD (15 doses)	500/100 mg BID	24	↔	1.09 (0.99, 1.19)	1.04 (0.97, 1.12)	1.02 (0.92, 1.12)
		750/200 mg BID (15 doses)	22	↔	1.12 (0.98, 1.28)	1.00 (0.93, 1.09)	0.94 (0.84, 1.04)
Ethinyl estradiol	0.035 mg (1 dose)	500/100 mg BID	21	↓	0.52 (0.47, 0.57)	0.52 (0.48, 0.56)	-
		750/200 mg BID (21 doses)	13	↓	0.48 (0.42, 0.57)	0.57 (0.54, 0.60)	-
Fluconazole	200 mg (Day 1) then 100 mg QD (6 or 12 doses)	500/200 mg BID (2 or 14 doses)	19	↔	0.97 (0.94, 1.01)	0.99 (0.97, 1.02)	0.98 (0.94, 1.02)
			19	↔	0.94 (0.91, 0.98)	0.92 (0.88, 0.95)	0.89 (0.85, 0.92)
Lopinavir/RTV[a]	400/100 mg BID (27 doses)	500/200 mg BID (28 doses)	21	↓	0.53 (0.40, 0.69)[d]	0.45 (0.32, 0.63)[d]	0.30 (0.17, 0.51)[d]
			69	↓	-	-	0.48 (0.40, 0.58)[e]
Loperamide	16 mg (1 dose)	750/200 mg BID (21 doses)	24	↓	0.39 (0.31, 0.48)	0.49 (0.40, 0.61)	-
N-Demethyl-Loperamide			24	↓	0.21 (0.17, 0.25)	0.23 (0.19, 0.27)	

[a]HIV+ patients
[b]HIV+ patients (TPV/ritonavir 250 mg/200 mg, 750 mg/200 mg and 1250 mg/100 mg) and healthy volunteers (TPV/ritonavir 500 mg/100 mg and 750 mg/200 mg)
[c]Normalized sum of parent drug (rifabutin) and active metabolite (25-O-desacetyl-rifabutin)
[d]Intensive PK analysis
[e]Drug levels obtained at 8-16 hrs post-dose

Table 5 Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of tipranavir/ritonavir (continued)

Co-administered Drug	Co-administered Drug Dose (Schedule)	TPV/ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Co-administered Drug Pharmacokinetic Parameters with/without TPV/ritonavir No Effect = 1.00		
					C_{max}	AUC	C_{min}
Lamivudine[a]	150 mg BID (43 doses)	250/200 mg BID	64	↔	0.96 (0.89, 1.03)	0.95 (0.89, 1.02)	-
		750/100 mg BID					
		1250/100 mg BID (42 doses)	46	↔	0.86 (0.78, 0.94)	0.96 (0.90, 1.03)	-
			35	↔	0.71 (0.62, 0.81)	0.82 (0.66, 1.00)	-
Nevirapine[a]	200 mg BID (43 doses)	250/200 mg BID	26	↔	0.97 (0.90, 1.04)	0.97 (0.91, 1.04)	0.96 (0.87, 1.05)
		750/100 mg BID	22	↔	0.86 (0.76, 0.97)	0.89 (0.78, 1.01)	0.93 (0.80, 1.08)
		1250/100 mg BID (42 doses)	17	↔	0.71 (0.62, 0.82)	0.76 (0.63, 0.91)	0.77 (0.64, 0.92)
Norethindrone	1.0 mg (1 dose)	500/100 mg BID	21	↔	1.03 (0.94, 1.13)	1.14 (1.06,1.22)	-
		750/200 mg BID (21 doses)	13	↔	1.08 (0.97, 1.20)	1.27 (1.13,1.43)	-
Rifabutin	150 mg (1 dose)	500/200 mg BID (15 doses)	20	↑	1.70 (1.49, 1.94)	2.90 (2.59, 3.26)	2.14 (1.90, 2.41)
25-O-desacetyl-rifabutin			20	↑	3.20 (2.78, 3.68)	20.71 (17.66, 24.28)	7.83 (6.70, 9.14)
Rifabutin + 25-O-desacetyl-rifabutin[c]			20	↑	1.86 (1.63, 2.12)	4.33 (3.86, 4.86)	2.76 (2.44, 3.12)
Saquinavir/RTV[a]	600/100 mg BID (27 doses)	500/200 mg BID (28 doses)	20	↓	0.30 (0.23, 0.40)[d]	0.24 (0.19, 0.32)[d]	0.18(0.13,0.26)[d]
			68	↓	-	-	0.20(0.16,0.25)[e]
Stavudine[a]	40 mg BID, ≥60 kg	250/200 mg BID	26	↔	0.90 (0.81, 1.02)	1.00 (0.91, 1.11)	-
		750/100 mg BID	22	↔	0.76 (0.66, 0.89)	0.84 (0.74, 0.96)	-
	30 mg BID, <60 kg (43 doses)	1250/100 mg BID (42 doses)	19	↔	0.74 (0.69, 0.80)	0.93 (0.83, 1.05)	-
Tenofovir	300 mg (1 dose)	500/100 mg BID	22	↓	0.77 (0.68, 0.87)	0.98 (0.91, 1.05)	1.07 (0.98, 1.17)
		750/200 mg BID (23 doses)	20	↓	0.62 (0.54, 0.71)	1.02 (0.94, 1.10)	1.14 (1.01, 1.27)
Zidovudine[b]	300 mg BID	250/200 mg BID	48	↓	0.54 (0.47, 0.62)	0.58 (0.51, 0.66)	-
	300 mg BID	750/100 mg BID	31	↓	0.51 (0.44, 0.60)	0.64 (0.55, 0.75)	-
	300 mg BID (43 doses)	1250/100 mg BID (42 doses)	23	↓	0.49 (0.40, 0.59)	0.69 (0.49, 0.97)	-
	300 mg (1 dose)	500/100 mg BID	29	↓	0.39 (0.33, 0.45)	0.57 (0.52, 0.63)	0.89 (0.81, 0.99)
		750/200 mg BID (23 doses)	25	↕	0.44 (0.36, 0.54)	0.67 (0.62, 0.73)	1.25 (1.08, 1.44)
Zidovudine glucuronide		500/100 mg BID	29	↑	0.82 (0.74, 0.90)	1.02 (0.97, 1.06)	1.52 (1.34, 1.71)
		750/200 mg BID (23 doses)	25	↑	0.82 (0.73, 0.92)	1.09 (1.05, 1.14)	1.94 (1.62, 2.31)

[a]HIV+ patients
[b]HIV+ patients (TPV/ritonavir 250 mg/200 mg, 750 mg/200 mg and 1250 mg/100 mg) and healthy volunteers (TPV/ritonavir 500 mg/100 mg and 750 mg/200 mg)
[c]Normalized sum of parent drug (rifabutin) and active metabolite (25-O-desacetyl-rifabutin)
[d]Intensive PK analysis
[e]Drug levels obtained at 8-16 hrs post-dose

INDICATIONS AND USAGE

APTIVUS® (tipranavir), co-administered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of APTIVUS/ritonavir of 24 weeks duration. Both studies were conducted in clinically advanced, 3-class antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with APTIVUS/ritonavir:

- The use of other active agents with APTIVUS/ritonavir is associated with a greater likelihood of treatment response (see **CLINICAL PHARMACOLOGY, Microbiology** and **INDICATIONS AND USAGE, Description of Clinical Studies**).

- Genotypic or phenotypic testing and/or treatment history should guide the use of APTIVUS/ritonavir (see **CLINICAL PHARMACOLOGY, Microbiology**). The number of baseline primary protease inhibitor mutations affects the virologic response to APTIVUS/ritonavir (see **CLINICAL PHARMACOLOGY, Microbiology**).

- Liver function tests should be performed at initiation of therapy with APTIVUS/ritonavir and monitored frequently throughout the duration of treatment (see **WARNINGS**).

- Use caution when prescribing APTIVUS/ritonavir to patients with elevated transaminases, hepatitis B or C co-infection or other underlying hepatic impairment (see **WARNINGS**).

- The extensive drug-drug interaction potential of APTIVUS/ritonavir when co-administered with multiple classes of drugs must be considered prior to and during APTIVUS/ritonavir use (see **CLINICAL PHARMACOLOGY** and **CONTRAINDICATIONS**).

- The risk-benefit of APTIVUS/ritonavir has not been established in treatment-naïve adult patients or pediatric patients.

There are no study results demonstrating the effect of APTIVUS/ritonavir on clinical progression of HIV-1.

Description of Clinical Studies

The following clinical data is derived from analyses of 24-week data from ongoing studies measuring effects on plasma HIV-1 RNA levels and CD4+ cell counts. At present there are no results from controlled studies evaluating the effect of APTIVUS/ritonavir on clinical progression of HIV.

Treatment-Experienced Patients

Studies 1182.12 and 1182.48: APTIVUS/ritonavir 500/200 mg BID + optimized background regimen (OBR) vs. Comparator Protease Inhibitor/ritonavir BID + OBR

Studies 1182.12 and 1182.48 are ongoing, randomized, controlled, open-label, multicenter studies in HIV-positive, triple antiretroviral class experienced patients. All patients were required to have previously received at least two protease inhibitor-based antiretroviral regimens and were failing a protease inhibitor-based regimen at the time of study entry with baseline HIV-1 RNA at least 1000 copies/mL and any CD4+ cell count. At least one primary protease gene mutation from among 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M had to be present at baseline, with not more than two mutations at codons 33, 82, 84 or 90.

These studies evaluated treatment response at 24 weeks in a total of 1159 patients receiving either APTIVUS co-administered with 200 mg of ritonavir plus OBR versus a control group receiving a ritonavir-boosted protease inhibitor (lopinavir, amprenavir, saquinavir or indinavir) plus OBR. Prior to randomization, OBR was individually defined for each patient based on genotypic resistance testing and patient history. The investigator had to declare OBR, comparator protease inhibitor, and use of enfuvirtide prior to randomization. Randomization was stratified by choice of comparator protease inhibitor and use of enfuvirtide.

After Week 8, patients in the control group who met the protocol defined criteria of initial lack of virologic response had the option of discontinuing treatment and switching over to APTIVUS/ritonavir in a separate roll-over study.

Demographics and baseline characteristics were balanced between the APTIVUS/ritonavir arm and control arm. In both studies combined, the 1159 patients had a median age of 43 years (range 17-80), were 88% male, 73% white, 14% black and 1% Asian. The median baseline plasma HIV-1 RNA was 4.82 (range 2 to 6.8) $\log_{10}$ copies/mL and median baseline CD4+ cell count was 155 (range 1 to 1893) cells/mm^3. Forty percent (40%) of the patients had baseline HIV-1 RNA of $\geq$ 100,000 copies/mL, 61% had a baseline CD4+ cell count < 200 cells/mm^3, and 57% had experienced an AIDS defining Class C event at baseline.

Patients had prior exposure to a median of 6 NRTIs, 1 NNRTI, and 4 PIs. A total of 12% of patients had previously used enfuvirtide. In baseline patient samples (n=454), 97% of the isolates were resistant to at least one protease inhibitor, 95% of the isolates were resistant to at least one NRTI, and > 75% of the isolates were resistant to at least one NNRTI.

The individually pre-selected protease inhibitor based on genotypic testing and the patient's medical history was lopinavir in 50%, amprenavir in 26%, saquinavir in 20% and indinavir in 4% of patients. A total of 86% were possibly resistant or resistant to the pre-selected comparator protease inhibitors. Approximately 25% of patients used enfuvirtide during study. There were differences between Studies 1182.12 and 1182.48 in the use of the protease inhibitors and in the use of enfuvirtide.

Treatment response and efficacy outcomes of randomized treatment through Week 24 of Studies 1182.12 and 1182.48 are shown in Table 6.

Table 6 Outcomes of Randomized Treatment Through Week 24 (Pooled Studies 1182.12 and 1182.48)

Outcome	Tipranavir/ritonavir (500/200 mg BID) + OBR (N = 582)	Comparator Protease Inhibitor*/ritonavir + OBR (N = 577)
Virological Responders[a] (confirmed at least 1 $\log_{10}$ HIV-1 RNA below baseline)	40%	18%
Virological failures	54%	79%
Initial lack of virologic response by Week 8[b]	35%	59%
Rebound	12%	11%
Never suppressed	7%	8%
Death[c] or discontinued due to adverse events	1%	1%
Discontinued due to other reasons[d]	5%	2%

*Comparator protease inhibitors were lopinavir, amprenavir, saquinavir or indinavir and 86% of patients were possibly resistant or resistant to the chosen protease inhibitors.

[a]Patients achieved and maintained a confirmed $\geq 1 \log_{10}$ HIV-1 RNA drop from baseline through Week 24 without prior evidence of treatment failure.

[b]Patients did not achieve a 0.5 log HIV-1 RNA drop from baseline and did not have viral load < 100,000 copies/mL by Week 8.

[c]Patients who died while being virologically suppressed.

[d]Includes patients who were lost to-follow-up, withdrawn consent, non-adherent, protocol violations, added/changed background antiretroviral drugs for reasons other than tolerability or toxicity, or discontinued while suppressed.

Through 24 weeks of treatment, the proportion of patients in the APTIVUS/ritonavir arm compared to the comparator PI/ritonavir arm with HIV-1 RNA < 400 copies/mL was 34% and 16% respectively, and with HIV-1 RNA < 50 copies/mL was 23% and 9% respectively. Among all randomized and treated patients, the median change from baseline in HIV-1 RNA at the last measurement up to Week 24 was -0.80 $\log_{10}$ copies/mL in patients receiving APTIVUS/ritonavir versus -0.25 $\log_{10}$ copies/mL in the comparator PI/ritonavir arm.

Among all randomized and treated patients, the median change from baseline in CD4+ cell count at the last measurement up to Week 24 was +34 cells/mm^3 in patients receiving tipranavir/ritonavir (N = 582) versus +4 cells/mm^3 in the comparator PI/ritonavir (N = 577) arm.

Patients in the APTIVUS/ritonavir arm achieved a significantly better virologic outcome when APTIVUS/ritonavir was combined with enfuvirtide (see **CLINICAL PHARMACOLOGY, Microbiology**).

CONTRAINDICATIONS

APTIVUS (tipranavir) is contraindicated in patients with known hypersensitivity to any of the ingredients of the product.

APTIVUS is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency (see **WARNINGS**).

Co-administration of APTIVUS with 200 mg of ritonavir with drugs that are highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. These drugs are listed in Table 7 below. For information regarding clinical recommendations see **PRECAUTIONS, Drug Interactions, Tables 8 and 9**.

Table 7 Drugs that are Contraindicated with Tipranavir, Co-Administered with 200 mg of Ritonavir

Drug Class	Drugs within Class that are Contraindicated with APTIVUS, Co-administered with 200 mg of ritonavir
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

Due to the need for co-administration of APTIVUS with 200 mg of ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

WARNINGS

ALERT: Find out about medicines that should NOT be taken with APTIVUS. This statement is included on the product's bottle label.

APTIVUS (tipranavir) must be co-administered with 200 mg of ritonavir to exert its therapeutic effect (see **DOSAGE AND ADMINISTRATION**). Failure to correctly co-administer APTIVUS with ritonavir will result in reduced plasma levels of tipranavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions (effect of tipranavir and ritonavir on other drugs).

Please refer to ritonavir prescribing information for additional information on precautionary measures.

Hepatic Impairment and Toxicity

APTIVUS co-administered with 200 mg of ritonavir, has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications. A causal relationship to APTIVUS/ritonavir could not be established. All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with APTIVUS/ritonavir, and frequently throughout the duration of treatment.

Patients with chronic hepatitis B or hepatitis C co-infection or elevations in transaminases are at approximately 2.5-fold risk for developing further transaminase elevations or hepatic decompensation. Additionally, Grade 3 and 4 increases in hepatic transaminases were observed in 6% of healthy volunteers in Phase 1 studies and 6% of subjects receiving APTIVUS/ritonavir in Phase 3 studies.

Tipranavir is principally metabolized by the liver. Therefore caution should be exercised when administering APTIVUS/ritonavir to patients with hepatic impairment because tipranavir concentrations may be increased. APTIVUS/ritonavir is contraindicated in patients with moderate to severe (Child-Pugh Class B and Child-Pugh Class C) hepatic insufficiency.

Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. Patients with signs or symptoms of clinical hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation.

For information on the multi-dose pharmacokinetics of tipranavir in hepatically impaired patients (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations,** ***Hepatic Impairment***).

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-1 infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

Sulfa Allergy

APTIVUS (tipranavir) should be used with caution in patients with a known sulfonamide allergy. Tipranavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs in the sulfonamide class and tipranavir is unknown.

Rash

Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported in subjects receiving APTIVUS/ritonavir. In Phase 2 and 3 trials rash was observed in 14% of females and in 8-10% of males receiving APTIVUS/ritonavir. Additionally, in one drug interaction trial in healthy female volunteers administered a single dose of ethinyl estradiol followed by APTIVUS/ritonavir, 33% of subjects developed a rash. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus has been reported in both men and women receiving APTIVUS/ritonavir (see **PRECAUTIONS, Drug Interactions** and **ADVERSE REACTIONS**).

Patients with Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional Factor VIII was given. In more than half of the reported cases, treatment with

protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship between protease inhibitors and these events has not been established.

Lipid Elevations

Treatment with APTIVUS co-administered with 200 mg of ritonavir has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS, Table 11**). Triglyceride and cholesterol testing should be performed prior to initiating APTIVUS/ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate (see **PRECAUTIONS, Drug Interactions, Table 9: Established and Other Potentially Significant Drug Interactions** for additional information on potential drug interactions with APTIVUS/ritonavir and HMG-CoA reductase inhibitors).

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tipranavir. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jeroveci* pneumonia, tuberculosis, or reactivation of herpes simplex and herpes zoster), which may necessitate further evaluation and treatment.

Information for Patients

Patients should be informed that APTIVUS co-administered with 200 mg of ritonavir, has been associated with severe liver disease, including some deaths. Patients with signs or symptoms of clinical hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation. Symptoms of hepatitis include fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. Extra vigilance is needed for patients with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity.

Liver function tests should be performed prior to initiating therapy with tipranavir and 200 mg of ritonavir, and frequently throughout the duration of treatment. Patients with chronic hepatitis B or C co-infection or elevations in liver enzymes prior to treatment are at increased risk (approximately 2.5-fold) for developing further liver enzyme elevations or severe liver disease. Caution should be exercised when administering APTIVUS/ritonavir to patients with liver enzyme abnormalities or history of chronic liver disease. Increased liver function testing is warranted in these patients. APTIVUS should not be given to patients with moderate to severe liver disease.

Mild to moderate rash has been reported in HIV-infected men and women receiving APTIVUS/ritonavir.

Women receiving estrogen-based hormonal contraceptives should be instructed that additional or alternative contraceptive measures should be used during therapy with APTIVUS/ritonavir. There may be an increased risk of rash when APTIVUS is given with hormonal contraceptives.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be informed that APTIVUS must be co-administered with 200 mg ritonavir to ensure its therapeutic effect. Failure to correctly co-administer APTIVUS with ritonavir will result in reduced plasma levels of tipranavir that may be insufficient to achieve the desired antiviral effect.

Patients should be told that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using APTIVUS. Patients should be advised to take APTIVUS and other concomitant antiretroviral therapy every day as prescribed. APTIVUS, co-administered with ritonavir, must be given in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of APTIVUS is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that APTIVUS is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of APTIVUS are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with APTIVUS can reduce the risk of transmitting HIV to others through sexual contact.

APTIVUS may interact with some drugs; therefore, patients should be advised to report to their health care provider the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

APTIVUS should be taken with food to enhance absorption.

The Patient Package Insert provides written information for the patients, and should be dispensed with each new prescription and refill.

Drug Interactions

Tipranavir administered with ritonavir can alter plasma exposure of other drugs and other drugs can alter plasma exposure of tipranavir and ritonavir.

Tipranavir co-administered with 200 mg of ritonavir at the recommended dosage is a net inhibitor of CYP 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP 3A. Thus, co-administration of tipranavir/ritonavir with drugs highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Co-administration with other CYP 3A substrates may require a dose adjustment or additional monitoring (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

The mechanisms of the potential interactions are described in the **CLINICAL PHARMACOLOGY, Drug Interactions** section.

Drugs that are contraindicated or not recommended for co-administration with APTIVUS are included in Table 8 below. These recommendations are based on either drug interaction studies or they are predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 8 Drugs that Should Not be Co-administered with APTIVUS Co-administered with 200 mg of Ritonavir

Drug Class/Drug Name	Clinical Comment
Antiarrhythmics Amiodarone, bepridil, flecainide, propafenone, quinidine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
Antihistamines Astemizole, terfenadine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials Rifampin	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
Ergot derivatives Dihydroergotamine, ergonovine, ergotamine, methylergonovine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products St. John's wort	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
HMG CoA reductase inhibitors Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptics Pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedatives/hypnotics Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

Clinically significant drug-drug interactions of APTIVUS co-administered with 200 mg of ritonavir are summarized in the Table 9 below.

Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)

Concomitant Drug Class: Drug name	Effect on Concentration of Tipranavir or Concomitant Drug	Clinical Comment
	Other Agents for Opportunistic Infections	
Antimycobacterials:		
Clarithromycin	↑ Tipranavir, ↑ Clarithromycin, ↓ 14-hydroxy-clarithromycin metabolite	No dose adjustment of tipranavir or clarithromycin for patients with normal renal function is necessary. For patients with renal impairment the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%.
Rifabutin	Tipranavir not changed, ↑Rifabutin ↑ Desacetyl-rifabutin	Single dose study. Dosage reductions of rifabutin by 75% are recommended (e.g. 150 mg every other day). Increased monitoring for adverse events in patients receiving the combination is warranted. Further dosage reduction may be necessary.
	Other Agents Commonly used	
Calcium Channel Blockers: Diltiazem Felodipine Nicardipine Nisoldipine Verapamil	Combination with TPV/ritonavir not studied. Cannot predict effect of TPV/ritonavir on calcium channel blockers that are dual substrates of CYP 3A and P-gp due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp. ↕ Diltiazem ↑ Felodipine (CYP 3A substrate but not P-gp substrate) ↕ Nicardipine ↕ Nisoldipine (CYP 3A substrate but not clear whether it is a P-gp substrate) ↕ Verapamil	Caution is warranted and clinical monitoring of patients is recommended.
Despiramine	Combination with TPV/ritonavir not studied ↑ Despiramine	Dosage reduction and concentration monitoring of despiramine is recommended.

Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)

Disulfiram/Metronidazole	Combination with TPV/ritonavir not studied	APTIVUS capsules contain alcohol that can produce disulfiram-like reactions when co-administered with disulfiram or other drugs which produce this reaction (e.g. metronidazole).
HMG-CoA reductase inhibitors:		Start with the lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors. Concomitant use of APTIVUS, co-administered with 200 mg of ritonavir, with lovastatin or simvastatin is not recommended.
Atorvastatin	↑ Tipranavir, ↑ Atorvastatin ↓ Hydroxy-atorvastatin metabolites	
Hypoglycemics:	Combination with TPV/ritonavir not studied.	Careful glucose monitoring is warranted.
Glimepiride Glipizide Glyburide Pioglitazone Repaglinide Tolbutamide	↕ Glimepiride (CYP 2C9) ↕ Glipizide (CYP 2C9) ↕ Glyburide (CYP 2C9) ↕ Pioglitazone (CYP 2C8 and CYP 3A4) ↕ Repaglinide (CYP 2C8 and CYP 3A4) ↕ Tolbutamide (CYP 2C9) The effect of TPV/ritonavir on CYP 2C8 and CYP 2C9 substrates is not known.	
Immunosuppressants:	Combination with TPV/ritonavir not studied. Cannot predict effect of TPV/ritonavir on immunosuppressants due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp.	More frequent concentration monitoring of these medicinal products is recommended until blood levels have been stabilized.
Cyclosporine Sirolimus Tacrolimus	↕ Cyclosporine ↕ Sirolimus ↕ Tacrolimus	
Narcotic analgesics:		
Meperidine	Combinations with TPV/ritonavir not studied ↓ Meperidine, ↑ Normeperidine	Dosage increase and long-term use of meperidine are not recommended due to increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (e.g. seizures).
Methadone	↓ Methadone by 50%	Dosage of methadone may need to be increased when co-administered with tipranavir and 200 mg of ritonavir.

Table 9 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction (continued)

Oral contraceptives/Estrogens: Ethinyl estradiol	↓ Ethinyl estradiol concentrations by 50%	Alternative methods of nonhormonal contraception should be used when estrogen based oral contraceptives are co-administered with tipranavir and 200 mg of ritonavir. Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency. Women using estrogens may have an increased risk of non serious rash.
PDE5 inhibitors: Sildenafil Tadalafil Vardenafil	Combinations with TPV/ritonavir not studied. ↑ Sildenafil ↑ Tadalafil ↑ Vardenafil	Concomitant use of PDE5 inhibitors with tipranavir and ritonavir should be used with caution and in no case should the starting dose of: • sildenafil exceed 25 mg within 48 hours • tadalafil exceed 10 mg every 72 hours • vardenafil exceed 2.5 mg every 72 hours
Selective Serotonin-Reuptake Inhibitors: Fluoxetine Paroxetine Sertraline	Combination with TPV/ritonavir not studied ↑ Fluoxetine ↑ Paroxetine ↑ Sertraline	Antidepressants have a wide therapeutic index, but doses may need to be adjusted upon initiation of APTIVUS/ritonavir therapy.
Warfarin	Combination with TPV/ritonavir not studied. Cannot predict the effect of TPV/ritonavir on S-Warfarin due to conflicting effect of TPV and RTV on CYP 2C9	Frequent INR (international normalized ratio) monitoring upon initiation of tipranavir/ritonavir therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal carcinogenicity bioassays with tipranavir and tipranavir/ritonavir are currently in progress. However, tipranavir showed no evidence of mutagenicity or clastogenicity in a battery of five *in vitro* and *in vivo* tests including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, unscheduled DNA synthesis in rat hepatocytes, induction of gene mutation in Chinese hamster ovary cells, a chromosome aberration assay in human peripheral lymphocytes, and a micronucleus assay in mice.

Tipranavir had no effect on fertility or early embryonic development in rats at dose levels up to 1000 mg/Kg/day, equivalent to a C_{max} of 258 μM in females. Based on C_{max} levels in these rats, as well as an exposure (AUC) of 1670 μM·h in pregnant rats from another study, this exposure was

approximately equivalent to the anticipated exposure in humans at the recommended dose level of 500/200 mg tipranavir/ritonavir BID.

Pregnancy

Teratogenic Effects, Pregnancy Category C.

Investigation of fertility and early embryonic development with tipranavir disodium was performed in rats, teratogenicity studies were performed in rats and rabbits, and pre- and post-natal development were explored in rats.

No teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits up to dose levels of 1000 mg/Kg/day and 150 mg/Kg/day tipranavir, respectively, at exposure levels approximately 1.1-fold and 0.1-fold human exposure. At 400 mg/Kg/day and above in rats, fetal toxicity (decreased sternebrae ossification and body weights) was observed, corresponding to an AUC of 1310 μM·h or approximately 0.8-fold human exposure at the recommended dose. In rats and rabbits, fetal toxicity was not noted at 40 mg/Kg/day and 150 mg/Kg/day, respectively, corresponding accordingly to $C_{max}/AUC_{0\text{-}24h}$ levels of 30.4 μM/340 μM·h and 8.4 μM/120 μM·h. These exposure levels (AUC) are approximately 0.2-fold and 0.1-fold the exposure in humans at the recommended dose.

In pre- and post-development studies in rats, tipranavir showed no adverse effects at 40 mg/Kg/day (~0.2-fold human exposure), but caused growth inhibition in pups and maternal toxicity at dose levels of 400 mg/Kg/day (~0.8-fold human exposure). No post-weaning functions were affected at any dose level.

There are no adequate and well-controlled studies in pregnant women for the treatment of HIV-1 infection. APTIVUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to APTIVUS, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Because of both the potential for HIV transmission and any possible adverse effects of tipranavir, mothers should be instructed not to breastfeed if they are receiving APTIVUS.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of APTIVUS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of APTIVUS in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

APTIVUS (tipranavir), co-administered with 200 mg of ritonavir, has been studied in a total of 1854 HIV-positive adults as combination therapy in clinical studies. Of these, 1397 patients received the dose of 500/200 mg BID. Seven hundred sixty one (761) adults, including 385 in the 1182.12 and 1182.48 Phase 3 pivotal studies, have been treated for at least 24 weeks.

In 1182.12 and 1182.48 in the APTIVUS/ritonavir arm, the most frequent AEs were diarrhea, nausea, fatigue, headache and vomiting. Adverse events leading to discontinuation were reported by 7.8% of the tipranavir-treated patients and 4.9% of the comparator arm patients.

Due to the need for co-administration of APTIVUS with 200 mg of ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

The most frequent clinical treatment-emergent adverse events reported in Phase 3 clinical studies (1182.12 and 1182.48) in adults are summarized in Table 10 below. Events of moderate to severe intensity (Grades 2-4) reported in at least 2% of highly treatment-experienced subjects in either treatment group are included.

Table 10 Percentage of Patients with Treatment Emergent Adverse Events of at Least Moderate Intensity (Grades 2-4) in ≥ 2% of Patients in Either Treatment Group[a]

	Phase 3 Studies 1182.12 and 1182.48 (24-weeks)	
	Tipranavir/ritonavir (500/200 mg BID) + OBR (n=746)	Comparator PI/ritonavir[b] + OBR (n=737)
Gastrointestinal Disorders		
Diarrhea	10.9%	9.4%
Nausea	6.7%	4.6%
Vomiting	3.4%	3.0%
Abdominal pain[c]	2.8%	3.7%
General Disorders		
Pyrexia	4.6%	4.3%
Fatigue	4.0%	3.9%
Asthenia	1.5%	2.3%
Infections and Infestations		
Bronchitis	2.9%	1.1%
Nervous System Disorders		
Headache	3.1%	3.1%
Psychiatric Disorders		
Depression	2.0%	3.0%
Insomnia	1.2%	2.6%
Respiratory, Thoracic and Mediastinal Disorders		
Cough	0.8%	2.2%
Skin and Subcutaneous Tissue Disorders		
Rash	2.0%	2.0%

[a]Excludes laboratory abnormalities that were Adverse Events
[b]Comparator PI/RTV: lopinavir/ritonavir 400/100 mg BID, indinavir/ritonavir 800/100 mg BID, saquinavir/ritonavir 1000/100 mg BID, amprenavir/ritonavir 600/100 mg BID
[c]Abdominal pain includes Preferred Terms "Abdominal pain" and "Abdominal pain upper"

Clinically meaningful adverse reactions in < 2% of adult patients (n=1397) treated with APTIVUS/ritonavir 500/200mg in Phase 2 and 3 trials listed below by body system:

Blood and Lymphatic System Disorders: anemia, neutropenia, thrombocytopenia

Gastrointestinal Disorders: abdominal distension, dyspepsia, flatulence, gastroesophageal reflux disease, pancreatitis

General Disorders: influenza like illness, malaise, pyrexia

Hepatobiliary Disorders: hepatitis, hepatic failure

Immune System Disorders: hypersensitivity

Infections and infestations: reactivation of herpes simplex and varicella zoster

Investigations: hepatic enzymes increased, liver function test abnormal, lipase increased, weight decreased

Metabolism and Nutrition Disorders: anorexia, decreased appetite, dehydration, diabetes mellitus, facial wasting, hyperamylasemia, hypercholesterolemia, hyperglycemia

Musculoskeletal and Connective Tissue Disorders: muscle cramp, myalgia

Nervous System Disorders: dizziness, neuropathy peripheral, somnolence

Psychiatric Disorders: insomnia, sleep disorder

Renal and Urinary Disorders: renal insufficiency

Respiratory, Thoracic and Mediastinal Disorders: dyspnea

Skin and Subcutaneous System Disorders: exanthem, lipoatrophy, lipodystrophy acquired, lipohypertrophy, pruritus

Laboratory Abnormalities

Treatment-emergent clinical laboratory abnormalities reported at 24 weeks in Phase 3 clinical studies (1182.12 and 1182.48) in adults are summarized in Table 11 below.

Table 11 Treatment Emergent Laboratory Abnormalities Reported in ≥ 2% of Adult Patients

		Studies 1182.12 and 1182.48 (24-weeks)	
	Limit	APTIVUS/ritonavir (500/200 mg BID) + OBR (n = 732)	Comparator PI/ritonavir + OBR* (n = 726)
Hematology			
WBC count decrease			
Grade 3-4	< 2.0 x $10^3/\mu L$	3.6%	5.4%
Chemistry			
Amylase			
Grade 3-4	> 2 x ULN	2.9%	4.8%
ALT			
Grade 2	> 2.5-5 x ULN	10.7%	5.4%
Grade 3	> 5-10 x ULN	3.1%	1.4%
Grade 4	> 10 x ULN	2.7%	0.4%
AST			
Grade 2	> 2.5-5 x ULN	6.0%	5.8%
Grade 3	> 5-10 x ULN	3.3%	1.0%
Grade 4	> 10 x ULN	0.7%	0.4%
ALT and/or AST			
Grade 2-4	> 2.5 x ULN	17.5%	9.9%
Cholesterol			
Grade 2	> 300 – 400 mg/dL	11.3%	4.3%
Grade 3	> 400 – 500 mg/dL	2.5%	0.3%
Grade 4	> 500 mg/dL	0.8%	0%
Triglycerides			
Grade 2	400 – 750 mg/dL	26.2%	14.7%
Grade 3	> 750 – 1200 mg/dL	12.8%	5.6%
Grade 4	> 1200 mg/dL	6.1%	3.4%

*Comparator PI/RTV: lopinavir/ritonavir 400/100 mg BID, indinavir/ritonavir 800/100 mg BID, saquinavir/ritonavir 1000/100 mg BID, amprenavir/ritonavir 600/100 mg BID

In clinical trials extending up to 48 weeks, the proportion of patients who developed Grade 2-4 ALT and/or AST elevations increased to 24.4% with APTIVUS/ritonavir and to 12.8% with CPI/ritonavir.

OVERDOSAGE

There is no known antidote for tipranavir overdose. Treatment of overdose should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. If indicated, elimination of unabsorbed tipranavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since tipranavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

DOSAGE AND ADMINISTRATION

General

The recommended dose of APTIVUS (tipranavir) Capsules is 500 mg (two 250 mg capsules), co-administered with 200 mg of ritonavir, twice daily.

APTIVUS Capsules, co-administered with 200 mg of ritonavir should be taken with food. Bioavailability is increased with a high fat meal.

HOW SUPPLIED

APTIVUS (tipranavir) Capsules 250 mg are pink, oblong soft gelatin capsules imprinted in black with "TPV 250". They are packaged in HDPE unit-of-use bottles with a child resistant closure and 120 capsules. (NDC 0597-0003-02)

APTIVUS capsules should be **stored in a refrigerator 2°-8°C (36°-46°F)** prior to opening the bottle. After opening the bottle, the capsules may be **stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)** and must be used within 60 days.

Store in a safe place out of the reach of children.

Address medical inquiries to: http://us.boehringer-ingelheim.com, (800) 542-6257 or (800) 459-9906 TTY.

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APTIVUS Capsules are covered by U.S. Patents 5,852,195; 6,147,095; 6,169,181 and 6,231,887

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Revision Date: June 21, 2005

Patient Information

Aptivus® (ap' · ti · vəs) (tipranavir) **Capsules, 250 mg**	**Boehringer Ingelheim**

ALERT: Find out about medicines that should not be taken with Aptivus. Please also read the section "WHO SHOULD NOT TAKE APTIVUS".

Read the Patient Information that comes with APTIVUS before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. You should stay under a doctor's care while taking APTIVUS.

What is the most important information I should know about APTIVUS?

Patients taking APTIVUS, together with 200 mg NORVIR® (ritonavir), may develop severe liver disease that can cause death. If you develop any of the following symptoms of liver problems, you should stop taking APTIVUS/ritonavir treatment and call your doctor right away: tiredness, general ill feeling or "flu-like" symptoms, loss of appetite, nausea (feeling sick to your stomach), yellowing of your skin or whites of your eyes, dark (tea-colored) urine, pale stools (bowel movements), or pain, ache, or sensitivity on your right side below your ribs. If you have chronic Hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems.

What is APTIVUS?

APTIVUS is a medicine called a "protease inhibitor" that is used to treat adults with Human Immunodeficiency Virus (HIV). APTIVUS blocks HIV protease, an enzyme which is needed for HIV to make more virus. When used with other anti-HIV medicines, APTIVUS may reduce the amount of HIV in your blood and increase the number of CD4+ cells. Reducing the amount of HIV in the blood may keep your immune system healthy, so it can help fight infection.

APTIVUS is always taken with NORVIR® (ritonavir) and at the same time as NORVIR When you take APTIVUS with NORVIR, you must always use at least 2 other anti-HIV medicines.

Does APTIVUS cure HIV or AIDS?

APTIVUS does not cure HIV infection or AIDS. The long-term effects of APTIVUS are not known at this time. People taking APTIVUS may still get infections or other conditions common in people with HIV (opportunistic infections). It is very important that you stay under the care of your doctor during treatment with APTIVUS.

Does APTIVUS lower the chance of passing HIV to other people?

APTIVUS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. Continue to practice safer sex. Use a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Never use or share dirty needles.

Ask your doctor if you have any questions about safer sex or how to prevent passing HIV to other people.

Who should not take APTIVUS?

Do not take APTIVUS if you:

- are allergic to tipranavir or any of the other ingredients in APTIVUS. See the end of this leaflet for a list of major ingredients.
- are allergic to ritonavir (NORVIR®)
- have moderate to severe liver problems
- take any of the following types of medicines because **you could have serious side effects:**
    - Migraine headache medicines called "ergot alkaloids". If you take migraine headache medicines, ask you doctor or pharmacist if any of them are "ergot alkaloids".
    - Halcion® (triazolam)
    - Hismanal® (astemizole)
    - Orap® (pimozide)
    - Propulsid® (cisapride)
    - Seldane® (terfenadine)
    - Versed® (midazolam)
    - Pacenone® (amiodarone)
    - Vascor® (bepridil)
    - Tambocor® (flecainide)
    - Rythmol® (propafenone)
    - Quinaglute dura® (quinidine)

What should I tell my doctor before I take APTIVUS?

Tell your doctor about all of your medical conditions, including if you:

- **have liver problems** or are infected with Hepatitis B or Hepatitis C. These patients may have worsening of their liver disease.
- **are allergic to sulfa medicines.**
- **have hemophilia.** APTIVUS may cause increased bleeding.
- **have diabetes.** APTIVUS may worsen your diabetes or high blood sugar levels.

- **are pregnant or planning to become pregnant.** It is not known if APTIVUS can harm your unborn baby. You and your doctor will need to decide if APTIVUS is right for you. If you take APTIVUS while you are pregnant, talk to your doctor about how you can be in the Antiretroviral Pregnancy Registry.

- **are breast-feeding.** Do not breast-feed if you are taking APTIVUS. You should not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. Talk with your doctor about the best way to feed your baby.

- **are using estrogens for birth control or hormone replacement.** Women who use estrogens for birth control or hormone replacement have an increased chance of developing a skin rash while taking APTIVUS. If a rash occurs, it is usually mild to moderate, but you should talk to your doctor as you may need to temporarily stop taking either APTIVUS or the other medicine that contains estrogen or female hormones.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. **APTIVUS and many other medicines can interact. Sometimes serious side effects will happen if APTIVUS is taken with certain other medicines (see "Who should not take APTIVUS?").**

- Some medicines cannot be taken at all with APTIVUS
- Some medicines will require a change in dosage if taken with APTIVUS
- Some medicines will require close monitoring if taken with APTIVUS.

Women taking birth control pills need to use another birth control method. APTIVUS makes birth control pills work less well.

Know all the medicines you take and keep a list of them with you. Show this list to all your doctors and pharmacists anytime you get a new medicine you take. They will tell you if you can take these other medicines with APTIVUS. **Do not start any new medicines while you are taking APTIVUS without first talking with your doctor or pharmacist.** You can ask your doctor or pharmacist for a list of medicines that can interact with APTIVUS.

How should I take APTIVUS?

- Take APTIVUS exactly as your doctor has prescribed. You should check with your doctor or pharmacist if you are not sure. **You must take APTIVUS at the same time as NORVIR® (ritonavir).** The usual dose is 500 mg (two 250 mg capsules) of APTIVUS, together with 200 mg (two 100 mg capsules or 2.5 mL of solution) of NORVIR, twice per day. APTIVUS with NORVIR must be used together with other anti-HIV medicines.

APTIVUS comes in a capsule form and you should **swallow APTIVUS capsules whole. Do not chew the capsules.**

- Always take APTIVUS with food.
- Do not change your dose or stop taking APTIVUS without first talking with your doctor.
- If you take too much APTIVUS, call your doctor or poison control center right away.
- If you forget to take APTIVUS, take the next dose of APTIVUS, together with NORVIR® (ritonavir), as soon as possible. Do not take a double dose to make up for a missed dose.

- It is very important to take all your anti-HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop working to fight HIV (drug resistance).
- When your APTIVUS supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short period of time. The HIV virus may develop resistance to APTIVUS and become harder to treat. You should NEVER stop taking APTIVUS or your other HIV medicines without talking with your doctor.

What are the possible side effects of APTIVUS?

APTIVUS may cause serious side effects, including:

- **liver problems, including liver failure and death.** Your doctor should do blood tests to monitor your liver function during treatment with APTIVUS. Patients with liver diseases such as Hepatitis B and Hepatitis C may have worsening of their liver disease with APTIVUS and should have more frequent monitoring blood tests.

- **rash.** Mild to moderate rash, including flat or raised rashes or sensitivity to the sun, have been reported in approximately 10% of subjects receiving APTIVUS. Some patients who developed rash also had joint pain or stiffness, throat tightness, or generalized itching.

- **increased bleeding in patients with hemophilia.** This can happen in patients taking APTIVUS or other protease inhibitor medicines.

- **diabetes and high blood sugar (hyperglycemia).** This can happen in patients taking APTIVUS or other protease inhibitor medicines. Some patients have diabetes before starting treatment with APTIVUS which gets worse. Some patients get diabetes during treatment with APTIVUS. Some patients will need changes in their diabetes medicine. Some patients will need new diabetes medicine.

- **increased blood fat (lipid) levels.** Your doctor should do blood tests to monitor your blood fat (triglycerides and cholesterol) during treatment with APTIVUS. Some patients taking APTIVUS have large increases in triglycerides and cholesterol. The long-term chance of having a heart attack or stroke due to increases in blood fats caused by APTIVUS is not known at this time.

- **changes in body fat.** These changes have happened in patients taking APTIVUS. and other anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects include diarrhea, nausea, vomiting, stomach pain, tiredness and headache. Women taking birth control pills may get a skin rash.

It may be hard to tell the difference between side effects caused by APTIVUS, by the other medicines you are also taking, or by the complications of HIV infection. For this reason it is very important that

you tell your doctor about any changes in your health. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

The list of side effects is **not** complete. Ask your doctor or pharmacist for more information.

How should I store APTIVUS?

- Store APTIVUS capsules in a refrigerator at approximately **36°F to 46°F (2°C to 8°C).** Once the bottle is opened, the contents must be used within 60 days. Patients may take the bottle with them for use away from home so long as the bottle remains at a temperature of approximately **59°F to 86°F (15°C to 30°C).** You can write the date of opening the bottle on the label. Do not use after the expiration date written on the bottle.

- **Keep APTIVUS and all medicines out of the reach of children.**

General advice about APTIVUS

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use APTIVUS for a condition for which it was not prescribed. Do not give APTIVUS to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about APTIVUS. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about APTIVUS that is written for health professionals.

For additional information, you may also call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906. You may also request information through the company website at http://us.boehringer-ingelheim.com.

What are the ingredients in APTIVUS?

Active Ingredient: tipranavir

Major Inactive Ingredients: dehydrated alcohol, polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.

Rx only

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EXHIBIT B
COPY OF U.S. PATENT 5,852,195

US005852195A

United States Patent [19]

Romines et al.

[11] Patent Number: 5,852,195

[45] Date of Patent: Dec. 22, 1998

[54] PYRANONE COMPOUNDS USEFUL TO TREAT RETROVIRAL INFECTIONS

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[73] Assignee: **Pharmacia & Upjohn Company**, Kalamazoo, Mich.

[21] Appl. No.: **809,224**

[22] PCT Filed: **May 4, 1995**

[86] PCT No.: **PCT/US95/05219**

§ 371 Date: **Nov. 4, 1996**

§ 102(e) Date: **Nov. 4, 1996**

[87] PCT Pub. No.: **WO95/30670**

PCT Pub. Date: **Nov. 16, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 349,361, Dec. 2, 1994, abandoned, which is a continuation of Ser. No. 238,817, May 6, 1994, abandoned.

[51] **Int. Cl.**[6] **C07D 417/12**; C07D 401/12; C07D 403/12; A61K 31/44

[52] **U.S. Cl.** **546/282.1**; 546/162; 544/264; 544/286; 544/316; 548/311.1; 549/292

[58] **Field of Search** 546/282.1

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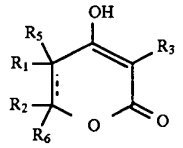
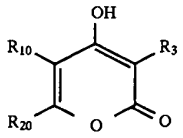
Primary Examiner—Alan L. Rotman
Attorney, Agent, or Firm—Martha A. Gammill; Lawrence T. Welch

[57] **ABSTRACT**

The present invention relates to compounds of formulae (I) and (II) which are pyran-2-ones, 5,6-dihydro-pyran-2-ones, 4-hydroxy-benzopyran-2-ones, 4-hydroxy-cycloalkyl[b] pyran-2-ones, and derivatives thereof, useful for inhibiting a retrovirus in a mammalian cell infected with said retrovirus, wherein R_{10} and R_{20} taken together are formulae (III) and (IV).



(I)



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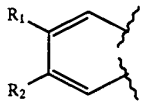

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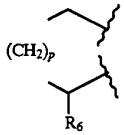

(IV)

5 Claims, No Drawings

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PYRANONE COMPOUNDS USEFUL TO TREAT RETROVIRAL INFECTIONS

CROSS-REFERENCE

This application is a 371 of PCT/US95/05219 filed May 4, 1995, which is a Continuation of U.S. Ser. No. 08/349,361 filed Dec. 2, 1994 (now abandoned), which is a Continuation of U.S. Ser. No. 08/238,817 filed May 6, 1994 (Abandoned).

The present invention relates to compounds useful for inhibiting a retrovirus in a human cell infected with said retrovirus. More particularly, the present invention provides pyran-2-ones, 5,6-dihydropyran-2-ones, 4-hydroxybenzopyran-2-ones, 4-hydroxy-cycloalkyl[b]pyran-2-ones, and derivatives thereof as HIV-proteinase inhibitors.

BACKGROUND OF THE INVENTION

During the past decade, acquired immunodeficiency syndrome (AIDS) has progressed from having the status of a medical curiosity afflicting only a small number of individuals to a problem of major proportions, both medically and economically. John Saunders and Richard Storer, "New Developments in RT Inhibitors," DN&P 5(3), April 1992, pages 153–169. WHO figures reveal that more than 360,000 cases of AIDS have been reported worldwide, including nearly 175,000 cases in the U.S.A. Of these, approximately 100,000 worldwide (50,000 in the U.S.A.) were reported in the preceding 12-month period. In the U.S.A., the number of seropositive individuals is thought to be approximately two million, and estimates suggest that 5–10 million people worldwide may be seropositive. Saunders and Storer, page 153.

Since the first description of the malady in the early part of this decade, acquired immunodeficiency disease syndrome (AIDS) and its devastating consequences have been subjects of continuous and intense coverage in both the lay and scientific press. Indeed, an edition of Scientific American was entirely devoted to AIDS (Scientific American 289, #4 (1988)), and the literature on the disease and the virus is already so vast as to defy thorough citation.

On Mar. 20, 1987, the FDA approved the use of the compound, zidovudine (AZT), to treat AIDS patients with a recent initial episode of pneumocystis carinii pneumonia, AIDS patients with conditions other than pneumocystis carinii pneumonia or patients infected with the virus with an absolute CD4 lymphocyte count of less than 200/mm^3 in the peripheral blood. AZT is a known inhibitor of viral reverse transcriptase, an enzyme necessary for human immunodeficiency virus replication. U.S. Pat. No. 4,724,232 claims a method of treating humans having acquired immunodeficiency syndrome utilizing 3'-azido-3'-deoxy-thymidine (azidothymidine, AZT).

Following the discovery of the anti-HIV activity of AZT, much effort has been focused on a wide variety of other dideoxynucleoside analogues in the search for superior agents. In the case of the 2'.3'-dideoxy series, ddC and ddI have shown potent activity against HIV in vitro and have been evaluated in clinical trials. Saunders and Storer, page 160. The compound ddC is currently being developed by Hoffman-La Roche Co. as a potential anti-AIDS drug. Its limiting toxicity in humans is peripheral neuropathy which is reversible at low doses. Raymond R. Schinazi, Jan R. Mead and Paul M. Feorino, "Insights Into HIV Chemotherapy," AIDS Research and Human Retroviruses, Vol. 8, Number 6, 1992, pages 963–990. It has been approved by the FDA for AIDS therapy in combination with AZT. The compound ddI has also been evaluated in clinical trials. Its limiting toxicities are peripheral neuropathy and pancreatitis. It has also been shown to stimulate hepatic glycolysis leading to irreversible liver damage. Schinazi, Mead and Feorino, page 966. It has recently been approved by the FDA for the treatment of HIV-1 infections in adults and pediatric patients who are intolerant to or whose health has significantly deteriorated while on AZT treatment. Schinazi, Mead and Feorino, page 966.

Among these approved drugs, AZT is currently the only drug that has been shown to decrease the mortality and frequency of opportunistic infections associated with AIDS. Schinazi, Mead and Feorino, page 963.

Human immunodeficiency virus (HIV) has long been recognized as the causative agent in AIDS, although a minority opinion to the contrary has been expressed (e.g., P. Duesberg, Proc. Natl. Acad. Sci., USA, 86:755–764 (1989)). Sequence analysis of the complete genomes from several infective and non-infective HIV-isolates has shed considerable light on the make-up of the virus and the types of molecules that are essential for its replication and maturation to an infective species. The HIV protease is essential for the processing of the viral gag and gag-pol polypeptides into mature virion proteins. L. Ratner, et al., Nature, 313:277–284 (1985); L. H. Pearl and W. R. Taylor, Nature, 329:351 (1987). HIV exhibits the same gag/pol/env organization seen in other retroviruses. L. Ratner, et al., above; S. Wain-Hobson, et al., Cell, 40:9–17 (1985); R. Sanchez-Pescador, et al., Science, 227:484–492 (1985); and M. A. Muesing, et al., Nature, 313:450–458 (1985).

Reverse transcriptase (RT) is an enzyme unique to retroviruses that catalyzes the conversion of viral RNA into double stranded DNA. Blockage at any point during the transcription process, by AZT or any other aberrant deoxynucleoside triphosphate incapable of elongation, should have dramatic consequences relative to viral replication. Much work on the RT target is in progress based, in large measure, upon the fact that nucleosides like AZT are easily delivered to cells. However, the inefficiency of phosphorylation steps to the triphosphate, and the lack of specificity and consequent toxicity, constitute major drawbacks to use of AZT and similar nucleosides having a blocked, or missing, 3'hydroxyl group.

The T4 cell receptor for HIV, the so-called CD4 molecule, has also been targeted as an intervention point in AIDS therapy. R. A. Fisher, et al., Nature, 331:76–78 (1988); R. E. Hussey, et al., Nature, 331:78–81 (1988); and K. C. Deen, et al., Nature, 331:82–84 (1988). The exterior portion of this transmembrane protein, a molecule of 371 amino acids (sCD4) has been expressed in Chinese hamster ovary (CHO) cells and Genentech (D. H. Smith, et al., Science, 238:1704–1707 (1987)) has had a product in clinical trials since the fall of 1987. CD4 has been shown to have a narrow spectrum of activity against wild-type virus and so far has failed to control HIV infection in humans. Schinazi, Mead and Feorino, page 963. The idea behind CD4 based therapy is that the molecules can neutralize HIV by interfering with viral attachment to T4, and other cells which express CD4 on their surfaces. A variant on this theme is to attach cell toxins to CD4 for specific binding and delivery to infected cells which display glycoprotein gp-120 on their surfaces. M. A. Till, et al., Science, 242:1166–1168 (1988); and V. K. Chaudhary, et al., Nature, 335:369–372 (1988).

Another therapeutic target in AIDS involves inhibition of the viral protease (or proteinase) that is essential for processing HIV-fusion polypeptide precursors. In HIV and several other retroviruses, the proteolytic maturation of the

gag and gag/pol fusion polypeptides (a process indispensable for generation of infective viral particles) has been shown to be mediated by a protease that is, itself, encoded by the pol region of the viral genome. Y. Yoshinaka, et al., Proc. Natl. Acad. Sci. USA, 82:1618–1622 (1985); Y. Yoshinaka, et al., J. Virol., 55:870–873 (1985); Y. Yoshinaka, et al., J. Virol., 57:826–832 (1986); and K. von der Helm, Proc. Natl. Acad. Sci., USA, 74:911–915 (1977). Inhibition of the protease has been shown to inhibit the processing of the HIV p55 in mammalian cell and HIV replication in T lymphocytes. T. J. McQuade, et al., Science, 247:454 (1990).

The protease (or proteinase), consisting of only 99 amino acids, is among the smallest enzymes known, and its demonstrated homology to aspartyl proteases such as pepsin and renin (L. H. Pearl and W. R. Taylor, Nature, 329:351–354 (1987); and I. Katoh, et al., Nature, 329:654–656 (1987)), led to inferences regarding the three-dimensional structure and mechanism of the enzyme (L. H. Pearl and W. R. Taylor, above) that have since been borne out experimentally. Active HIV protease has been expressed in bacteria (see, e.g., P. L. Darke, et al., J. Biol. Chem., 264:2307–2312 (1989)) and chemically synthesized (J. Schneider and S. B. Kent, Cell, 54:363–368 (1988); and R. F. Nutt, et al., Proc. Natl. Acad. Sci., USA, 85:7129–7133 (1988)). Site directed mutagenesis (P. L. Darke, et al., above); and N. E. Kohl, et al., Proc. Natl. Acad. Sci., USA, 85:4686–4690 (1988)) and pepstatin inhibition (P. L. Darke, et al., J. Biol. Chem., 264:2307–2312 (1989); S. Seelmeier, et al., Proc. Natl. Acad. Sci., USA, 85:6612–6616 (1988); C.-Z. Giam and I. Borsos, J. Biol. Chem., 263:14617–14720 (1988); and J. Hansen, et al., EMBO J., 7:1785–1791 (1988)) have provided evidence for HIV protease's mechanistic function as an aspartyl protease. A study has demonstrated that the protease cleaves at the sites expected in peptides modeled after the regions actually cleaved by the enzyme in the gag and pol precursor proteins during viral maturation. P. L. Darke, et al., Biochem. Biophys. Res. Communs., 156:297–303 (1988). X-ray crystallographic analysis of the HIV-protease (M. A. Navia, et al., Nature, 337:615–620 (1989)) and a related retroviral enzyme from Rous sarcoma virus (M. Miller, et al., Nature, 337:576–579 (1989)) reveal an active site in the protease dimer that is identical to that seen in other aspartyl proteases, thus supporting the supposition (L. H. Pearl and W. R. Taylor, above) that the HIV enzyme is active as a dimer. See also Joseph A. Martin, "Recent Advances in the Design of HIV Proteinase Inhibitors," Antiviral Research, 17 (1992) 265–278.

To date, the scientific search for a fully effective and safe means of inhibiting retroviruses in a human hosting such a virus, and thereby effectively treating diseases caused by such a virus, such as acquired immunodeficiency syndrome (AIDS), continues.

INFORMATION DISCLOSURE

JO 3227-923-A (Sawai Seiyaku KK) discloses the use of 4-hydroxy-coumarins as therapeutic agents for HIV-infected patients; however, unsubstituted 4-hydroxy-coumarin is the only compound specifically disclosed for this use.

WO 91/04663 (Univ. of Calif. at Oakland) discloses 6-amino-1,2-benzopyrones which are useful for treating viral diseases.

WO 91/12804 (Kabi Pharmaceutical), published 5 Sep. 1991, discloses the use of N-phenyl-N-methyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-quinoline-3-carboxamide also known as Linomide®, for the treatment of retrovirus infections.

International Publication No. WO 89/07939, published 8 Sep. 1989, discloses specific coumarin compounds which are reverse transcriptase inhibitors.

U.S. Pat. Nos. 3,489,774 and 3,493,586 disclose 3-(beta-aryl-beta-(arylthio) (or aryl seleno) propionyl-coumarin and pyrone products useful as parasiticides.

Biochemical and Biophysical Research Communications, Vol. 188, No. 2, 1992, pages 631–637, discloses chromones bearing hydroxyl substituents and a phenolic group at the 2-position (flavones) as having anti-HIV-1 proteinase activity.

Antimicrobial Patent Fast-Alert, Week Ending 4 Sep. 1992, disclose gamma-pyrones, gamma-pyridones and gamma-thio-pyrones as antiviral agents.

International Publication Nos. WO 92/04326, 92/04327 and 92/04328, all published 19 Mar. 1992, disclose antiviral heterocyclic derivatives, such as quinolinones and benzopyranones, as replication inhibitors for treating herpes simples 1 and 2, cytomegalovius and Epstein-Barr virus.

C.A. Selects: Antitumor Agents, Issue 19, 1992, page 25, No. 117:90147q (PCT International Application WO 92 06,687) discloses the preparation of 5-iodo-5-amino-1,2-benzopyrones and analogs as cytostatic and antiviral agents.

Nowhere do these references teach or suggest the use of 4-hydroxy-α-pyrones as HIV protease inhibitors or as having antiviral activity.

Phytochemistry, 31(3):953–956 (1992), discloses compounds, such as 4-hydroxy-α-(4-methoxyphenyl)-6-[2-(4-methoxyphenyl)ethenyl]-2-oxo-, methyl ester, (E)-(−)-2H-pyran-3-acetic acid.

Tetrahedron, 48(9):1695–1706 (1992), (see also Tetrahedron Lett., 30(23):3109–12 (1989)), discloses compounds, such as 3-[1-(4-chlorophenyl)-3-(4-nitrophenyl)-2-propenyl]-4-hydroxy-6-methyl-2H-pyran-2-one; 3-[3-(4-chlorophenyl)-1-(4-nitrophenyl)-2-propenyl]-4-hydroxy-6-methyl-2H-pyran-2-one; 4-hydroxy-3-[3-(4-methoxyphenyl)-1-(4-nitrophenyl)-2-propenyl]-6-methyl-2H-pyran-2-one; and 4-hydroxy-3-[1-(4-methoxyphenyl)-3-(4-nitrophenyl)-2-propenyl]-6-methyl-2H-pyran-2-one.

Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 30:17–24 (1988), discloses compounds, such as 4-hydroxy-β-(4-methoxyphenyl)-6-[2-(4-methoxyphenyl)ethenyl]-2-oxo-, methyl ester, (E)-(−)-2H-pyran-3-propanoic acid.

Chem. Absts. 53:15072f discloses compounds, such as α-1,3-dihydroxy-2-butenylidene-β-ethyl-, δ-lactone, hydrocinnamic acid.

Chem. Absts. 53:15072c discloses compounds, such as α-1,3-dihydroxy-2-butenylidene-β-isopropyl-, δ-lactone, hydrocinnamic acid.

Arch. Pharm. (Weinheim, Ger.), 316(12):988–94 (1983), discloses compounds, such as 3-[1-(4-chlorophenyl)-3-oxobutyl]-4-hydroxy-6-methyl-2H-pyran-2-one; and 3-[1-(4-chlorophenyl)propyl]-4-hydroxy-6-methyl-2H-pyran-2-one.

Chem. Ber., 110(3):1047–57 (1977), discloses compounds, such as 6-(3,4-dimethoxyphenyl)-3-[2-(3,4-dimethoxy-phenyl)-1-(4-methoxy-2-oxo-2H-pyran-6-yl) ethyl]-4-hydroxy-2H-pyran-2-one; and 3-[2-(3,4-dimethoxyphenyl)-1-(4-methoxy-2-oxo- 2H-pyran-6-yl) ethyl-4-hydroxy-6-[2-(4-methoxyphenyl)ethyl]-2H-pyran-2-one.

J. Heterocycl. Chem., 23(2):413–16 (1986), discloses compounds, such as 3-[(4-chlorophenyl)-1-piperidinylmethyl]-4-hydroxy-6-methyl-2H-pyran-2-one.

The following published PCT applications disclose peptides useful as retroviral protease inhibitors: International

Publication No. WO 91/06561, published 16 May 1991; and International Publication No. WO 92/17490, published 15 Oct. 1992.

The following references disclose pyrone compounds which are believed to be representative of those known in the art:

EP-443449 (German language) discloses 3-hexyl-5,6-dihydro-6-pentyl-2H-pyran-2-one and 3-ethyl-6-hexadecyl-5,6-dihydro-4-hydroxy-2H-pyran-2-one. Pestic. Sci., 27(1): 45–63 (1989), discloses 5,6-dihydro-4-hydroxy-6-methyl-6-(1-methyl-1-propenyl)-3-(1-oxobutyl)-2H-pyran-2-one; and 6-cyclopropyl-5,6-dihydro-4-hydroxy-6-methyl-3-(1-oxobutyl)-2H-pyran-2-one. Acta. Chem. Scand., 43(2): 193–95 (1989), discloses 4-(acetyloxy)-5,6-dihydro-3,6-dimethyl-2H-pyran-2-one. J. Org. Chem., 54(14):3383–9 (1989), discloses 5,6-dihydro-4-hydroxy-3,6,6-trimethyl-2H-pyran-2-one. J. Org. Chem., 53(6):1218–21 (1988); and Tetrahedron Lett., 34(2):277–80 (1993), discloses 3-hexyldihydro-6-undecyl-2H-pyran-2,4 (3H)-dione, (6R)-. J. Chem. Soc. Perkins Trans., 1(6):1157–9 (1985), discloses dihydro-3-methyl-6-nonyl-6-[[(tetrahydro-2H-pyran-2-yl) oxy]methyl]-2H-pyran-2,4 (3H)-dione. J. Chem. Ecol., 9(6) :703–14 (1983), discloses 5,6-dihydro-4-hydroxy-3,6-dimethyl-2H-pyran-2-one. J. Org. Chem., 48(7):1123–5 (1983), discloses 6-(2-chloro-1-methylethenyl-5,6-dihydro-4-hydroxy-3-methyl-2H-pyran-2-one, (Z)-(.+–.)-. Acta. Chem. Scand., 43(2):193–95 (1989); and Tetrahedron Lett., 21(6):551–4 (1980), discloses 5,6-dihydro-4-hydroxy-3,6-dimethyl-2H-pyran-2-one. Helv. Chem. Acta, 59(7) :2393–2401 (1976), discloses 4-[(3,6-dihydro-4-hydroxy-5-methyl-6-oxo-2H-pyran-2-yl)methyl]-2,6-piperidinedione. Acta. Chem. Scand., 30(7):613–18 (1976); and Tetrahedron Lett., 22:1903–4 (1976), discloses 5,6-dihydro-4-hydroxy-3-methyl-6-(1-methyl-1-propenyl)-2H-pyran-2-one, (E)-. 3,3'-[(4-nitrophenyl)methylene]bis[5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one; and 3,3'-(phenylmethylene)bis [5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one are disclosed in Synth. Commun., 20(18):2827–2836, 1990.

WO 93/07868, published 29 Apr. 1993, discloses new nitroso-benzopyrone, -benzamide and -isoquinolinone derivatives as adenosine di-phospho:ribose transferase inhibitors for treating viral infections and cancer.

WO 93/07128, published 15 Apr. 1993, relates to substituted cyclic carbonyls and derivatives thereof useful as retroviral protease inhibitors.

J. Indian Chem. Soc., 69:397–398 (July 1992), discloses that coumarin-4-acetic acids were screen for their anticancer and anti-AIDS activities and were found to be inactive.

The Journal of Antibiotics, 46(7):1126 (July 1993), discloses germicidin, which is 6-(2-butyl)-3-ethyl-4-hydroxy-2-pyrone, to be an autoregulative germination inhibitor of *Streptomyces viridochromogenes* NRRL B-1551.

Derwent Abstracts, 93-168920/21 of EP 543201 discloses the use of coumarin derivatives, such as 1-(N-morpholyl)-6-(4-hydroxybenzoic acid ethyl ester) hexane, for the treatment of viral infections, such as influenza or acute rhinitis.

J. Org. Chem., 48(22):3945–7 (1983); and Chem. Pharm. Bull., 29(10):2762–8 (1981); disclose compounds such as 4-hydroxy-6-(3-pyridinyl)-2H-pyran-2-one.

J. Labelled Compd. Radiopharm., 28(10):1143–8 (1990), discloses compounds such as 4-hydroxy-6-methyl-2H-pyran-2-one.

J. Am. Chem. Soc., 113(25):9585–95 (1991), discloses compounds such as 3-(3-phenyl-2-propen-1-yl)-6-methyl-4-hydroxy-2H-pyran-2-one.

CA 54:14239d and CA 53:4272c disclose compounds such as α-(α,γ-dihydroxycinnamylidene)-, δ-lactone hydrocinnamic acid.

CA 53:15072f discloses compounds such as α-1,3-dihydroxy-2-butenylidene-β-ethyl-, δ-lactone hydrocinnamic acid.

Synth. Commun., 20(18):2827–36 (1990), discloses compounds such as 3,3'-[(4-nitrophenyl)methylene]bis[5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one, and 3,3'-(phenylmethylene)bis[5,6-dihydro-4-hydroxy-6-methyl-2H-pyran-2-one.

J. Org. Chem., 54(14):3383–9 (1989), discloses compounds such as 5,6-dihydro-4-hydroxy-3,6,6-trimethyl-2H-pyran-2-one.

Derwent Abstract, 92-166863/20, of EP 553248 discloses new optionally substituted 5-iodo-6-amino-1,2-benzopyrone derivatives, which are adenosine di:phosphoribose inhibitors, for treatment and prevention of viruses and tumors associated with AIDS.

Synthesis of Heterocycles. XV. 4-Hydroxy-2-pyronocyclenes. E. Ziegler, H. Junek, and E. Nolken, Monatsh., 89:678–82 (1958) (CA 53:12283–4) discloses compounds such as the following: 4-hydroxy-3-benzyl-5,6-octamethylene-2-pyrone; 4-hydroxy-3-benzyl-5,6-pentamethylene-2-pyrone; 4-hydroxy-3-benzyl-5,6-heptamethylene-2-pyrone; 4-hydroxy-3-benzyl-5,6-hexamethylene-2-pyrone; and 4-hydroxy-3-benzyl-5,6-tridecamethylene-2-pyrone.

R. Effenberberger, T. Ziegler, K.-H. Schonwalder, T. Kesmarszky, B. Bauer, Chem. Ber 119:3394–3404 (1986), discloses pyrone intermediates, such as those of formula J-1 (wherein n is 4; refer to Chart J below).

Monatsh. Chem., 119(6–7):727–37 (1988) (CA 110(13): 114430k) discloses the compounds 8H-acenaphtho[1,2-b] pyran-8-one, 10-hydroxy-9-(phenylmethyl)-; and indeno[2, 1-b]pyran-3(5H)-one, 1-hydroxy-2-(phenylmethyl)-.

CA 54:14239b discloses the compound 3-benzyl-4-hydroxy-2-oxoindeno-[1,2-b]pyran.

Monatsh. Chem., 113(4):475–84 (1982) discloses compounds such as 6,7-dihydro-4-hydroxy-6-(3-methylphenyl)-7-phenyl-3-(phenylmethyl)-pyrano[2,3-c]pyrrole-2,5-dione; and 6,7-dihydro-4-hydroxy-6,7-diphenyl-3-(phenylmethyl)-pyrano[2,3-c]pyrrole-2,5-dione.

Monatsh. Chem. 90:594–9 (1959) (CA 54:14238g,h) discloses compounds such as 5H-benzocycloheptene-8-acrylic acid, α-benzyl-6,7-dihydro-β,-9-dihydroxy-,δ-lactone; and 3-benzyl-5,6,7,8-tetrahydro-4-hydroxy-8-isopropyl-5-methyl-coumarin.

Bull. Soc. Chim. Fr. 5:1719–23 (1069) (Fr) (CA 71(21): 101655p) discloses the compound 3-benzyl-5,6,7,8-tetrahydro-4-hydroxy-coumarin.

WO 8804652 (equivalent AU 8810440 (Jap.)) discloses the compound 3-(4-chloro-2-nitrobenzoyl)-5,6,7,8-tetrahydro-4-hydroxy-2H-1-benzopyran-2-one.

Monatsh. 92:246–53 (1961) (Gr) (CA 55:27296d) discloses the compound 3-(3,5-dimethylsalicyl)-5,6,7,8-tetrahydro-4-hydroxy-coumarin.

CA 94(9):65472r discloses 5,6,7,8-hexahydro-3-phenyl-2-H-cycloocta[b]pyran-2-one; and 6,7,8,9-tetrahydro-4-hydroxy-3-phenyl-cyclohepta[b]pyran-2(5H)-one.

J. Org. Chem. 28(11):3112–14 (1963) (CA 59:15185e) discloses the compound hexanedioic acid, 2-[hydroxy(2-hydroxy-1-cyclopenten-1-yl)methylene]-, δ-lactone.

Antimicrobial Patent Fast-Alert, Week Ending 30 Apr. 1993, discloses cyclic ureas and analogues useful as retroviral protease inhibitors.

Many 4-hydroxy-coumarin type compounds are known. For example, these references—CA 54:577e,g,h (1960); U.S. Pat. No. 2,872,457 (CA 53:12305e (1959)); CA 51:14826f,h (1957); U.S. Pat. No. 2,723,276 (CA 52:5480g,h (1958)); CA 51:14827a,b (1957); CA 51:16453a (1957); CA 54:5699d (1960); CA 54:16450f (1960); CA 53:22454a (1959); and CA 53:20046a—disclose compounds such as the following: 4-hydroxy-3-(1-phenylbutyl)-coumarin; 4-hydroxy-3-(1-phenylpentyl)-coumarin; 3-(cyclohexylphenylmethyl)-4-hydroxycoumarin; 4-hydroxy-3-(2-methyl-1-phenylpropyl)-coumarin; 4-hydroxy-3-(2-phenylpropyl) coumarin; 4-hydroxy-3-(1,3-diphenylpropyl)-coumarin; 4-hydroxy-3-(1-(4-methylphenyl)-butyl)-coumarin; 4-hydroxy-3-(1-(1-naphthyl)-propyl)-coumarin; 4-hydroxy-7-methyl-3-(1-phenylpropyl)-coumarin; 7-chloro-4-hydroxy-3-(1-phenylpropyl)-coumarin; 4-hydroxy-3-[1-(4-methoxyphenyl)propyl]-coumarin; 3-(.alpha.-ethyl-p-fluorobenzyl)-4-hydroxy-coumarin; 3-(α-ethyl-p-methoxybenzyl)-4-hydroxy-coumarin; and 3-(1-phenyl-propenyl)-4-hydroxy-coumarin.

To the best of our knowledge, from our review, these references do not disclose the use of these compounds as HIV protease inhibitors. They are disclosed as being useful as: rodenticides, lowering the prothrombin level of the blood, blood anticoagulants, and pesticides.

Additional 4-hydroxy-coumarin compounds with similar uses have been disclosed in the following references:

Indian J. Chem., Sect. B, 25B: 1167–70 (1986) (CA 107(17):154201f) and CA 93(23):220546t discloses the compound 4-Hydroxy-3-(1-phenyl-2-propenyl)-coumarin.

CA 96(19):157432x; CA 90(1):1707f; CA 84(9):55338f; CA 79(13):74969a; and CA 71(15):69677j disclose the compound 4-hydroxy-3-[1-(1,2,3,4-tetrahydro)naphthyl]-coumarin; CA 54:579e discloses the compound 4-hydroxy-3-[1-indanyl]-coumarin; CA 63:14743c discloses the compound 4-hydroxy-3-(1-naphthylmethyl)-coumarin; CA 63:5589c discloses the compound 3-(1'-(2-methoxy,3-methyl,5-chloro-phenyl)propyl)-4-hydroxy-coumarin; CA 64:12969b discloses the compound 3-(α-acetonyl-α-acetylbenzyl)-4-hydroxy-coumarin.

CA 79(13):74969a; Chim. Ther. 7(4):300–6 (1972) (Fr) (CA 78(7):38016h); CA 52:5399b; CA 54:5699e; CA 54:579e; and CA 72(15):78882v disclose 4-hydroxycoumarin compounds substituted at the 6- or 7-position by, e.g., methyl, methoxy and chloro.

J. M. Mulder, U.S. Pat. No. 3,835,161, 10 Sep. 1974, discloses the compound 3-[1-[4-(2-bromoethyl)phenyl] ethyl]-4-hydroxy-2H-1-benzopyran-2-one.

Merck Index, Eleventh Edition, (1989), Entry 9950, discusses Warfarin, its chemical name—3-α-phenyl-β-acetylethyl-4-hydroxycoumarin—and its uses as a rodenticide and an anticoagulant. J. Med. Chem., 1978, Vol. 21, No. 2:231–234, discloses the antivitamin K activity of warfarin and discusses the anticoagulant activity of several 3-substituted 4-hydroxycoumarins such as 4-Hydroxy-3-(1-phenylbutyl)-coumarin; and 4-hydroxy-3-(α-methylbenzyl)- coumarin. J. Am. Chem. Soc. 83:2676–9 (1961) (CA 55:22306e (1961)) discusses the resolution and absolute configuration of warfarin and discloses the preparation of compounds such as 4-hydroxy-3-(1-phenylbutyl)-coumarin.

Journal of Labelled Compounds and Radiopharmaceuticals Vol. XXIII, No. 2:137–148 (1986), discloses several deuterium labelled metabolites of warfarin and phenprocoumon, such as the deuterium labelled analog of the compound 4-hydroxy- 7-methoxy-3-(1-phenylpropyl)-coumarin.

J48023942 discloses compounds, such as 4-hydroxy-3-(α-methylbenzyl)-coumarin; 4-hydroxy-3-(3-methyl-1-phenylbutyl)-coumarin; and 2H-1-benzopyran-2-one, 4-hydroxy-7-methoxy-3-(1-phenylpropyl)-(also cited in preceding reference) and their use as rodenticides.

Tr. Voronezh. Teckhnol. Inst. 19(2):27–30 (1971), Abstract No. 1zh274 (Russian language), discloses the compound 4-hydroxy-3-phenethylcoumarin. This reference and Helv. Chim. Acta 74(7):1451–8 (1991) disclose the compound of 4-hydroxy-3-(3-phenylpropyl)coumarin.

J. Org. Chem. 33(1):437–8 (1968); and Eur. J. Med. Chem.—Chim Ther. 12(2):125–30 (1977) disclose compounds such as 4-hydroxy-3-diphenylmethylcoumarin.

U.S. Pat. No. 3,764,693 discloses the compound 4-hydroxy-3-(3-hydroxy-1-phenylbutyl)-coumarin and its anticoagulating and rodenticidal activity.

J. Med. Chem. 18(5):513–19 (1975) (CA 83(5):37913q); J. Chromatogr. 338(2):325–34 (1985); J. Chromatogr. 562 (1–2):31–8 (1991); J. Labelled Compds. Radiopharm. 23(2): 137–48 (1986) (cited previously); and J. Chromatogr. 529 (2):479–85 (1990) disclose compounds such as 4-hydroxy-3-[1-[3-(phenylmethoxy)phenyl]propyl]-2H-1-benzopyran-2-one; 4-hydroxy-8-(phenylmethoxy)-3-(1-phenylpropyl)-2H-1-benzopyran-2-one; 4-hydroxy-3-[1-(4-hydroxyphenyl)propyl]-coumarin; 4-hydroxy-6-methoxy-3-(1-phenylpropyl)-coumarin; 4,7-dihydroxy-3-(1-phenylpropyl)-coumarin; 4,6-dihydroxy-3-(1-phenylpropyl)- coumarin; 4-hydroxy-3-[1-(3-hydroxyphenyl)propyl]-coumarin; and p-chlorophenprocoumon.

AIDS 1993, Vol. 7, No. 1, pages 129–130, discusses the effect of warfarin on HIV-1 replication and spread.

CA Selects: AIDS & Related Immunodeficiencies, Issue 24, 1993, Abstract 119:195147j discloses the inhibitory effect of a single dose of coumarin derivatives, warfarin, 4-hydroxy-coumarin, umbelliferone, on HIV-1 replication and cell-mediated or cell-free viral transmission.

At the First National Conference on Human Retroviruses and Related Infections, 12–16 Dec. 1993, Washington, D.C., it was disclosed that coumarins, such as warfarin, and pyrones, such as 3-(thiophenyl)-6-phenyl-4-hydroxy-pyrone, displayed HIV protease inhibition in an assay.

Biochemical and Biophysical Research Communications, Vol. 201, No. 1, pages 290–294 (30 May 1994) discloses that warfarin and structurally related coumarin analogs are HIV-1 protease inhibitors.

J. Med. Chem. 37:2664–2677 (1994) discloses 4-hydroxy-3-(3-phenoxypropyl)-2H-1-benzopyran-2-one and structural analogs, especially 4,7-dihydroxy-3-[4-(2-methoxyphenyl)butyl]-2H-1-benzopyran-2-one, as HIV-1 protease inhibitors.

Biochemical and Biophysical Research Communications, Vol. 200, No. 3, pages 1658–1664 (16 May 1994) discloses that 4-hydroxy-3-(3-phenoxypropyl)-1-benzopyran-2-one and 4-hydroxy-6-phenyl-3-(phenylthio)-pyran-2-one, and structural analogs of these compounds, are inhibitors of HIV-1 protease.

J. Am. Chem. Soc. 116:6989–6990 (1994) discloses 4-hydroxy-6-phenyl-3-(phenylthio)pyran-2-one, and structural analogs thereof, are HIV-1 protease inhibitors.

Acta. Virol. 37:241–250 (1993) discloses the anti-HIV activity of coumarin derivatives, warfarin, 4-hydroxy-coumarin and umbelliferone.

Antiviral Research 24:275–288 (1994) discloses bicyclic imidazo derivatives (imidazothiazoles and

imidazopyridines) which inhibit HIV-1 through interaction with reverse transcriptase (RT).

U.S. Pat. No. 3,325,515 (J. Schmitt, et al.) discloses coumarin derivatives, such as 3-(4-hydroxy-3-coumarinyl)-3-phenyl-1-propionic acid methyl ester, as exhibiting anti-coagulant activity.

U.S. Pat. No. 2,723,277 (A. Grussner, et al.) discloses malonic acid derivatives, such as 3-[1'-(p-chloro-phenyl)-propyl]-4-hydroxy-coumarin, as anti-coagulant agents.

FR, A, 1276654 discloses 4-hydroxy-coumarins, such as (2'-hydroxy)-3-benzyl-4-hydroxycoumarin, which have anti-coagulant, anti-bacterial or anti-fungal properties.

BE, A, 674997 discloses 4-hydroxycoumarin derivatives, such as 3-(5-methoxytetralyl-(1))-4-hydroxycoumarin as agents for fighting rodents.

GB, A, 734142 discloses the preparation of 3-substituted-4-hydroxycoumarins, such as 3-(1-phenyl-2-acetyl)-ethyl-4-hydroxycoumarin and 3-(1-furan-2-acetyl)-ethyl-4-hydroxycoumarin, which are effective as anti-coagulants and rodenticides.

"The Application of Computer-Assisted Drug Design in the discovery of Nonpeptide HIV-1 Protease Inhibitors", Parke-Davis Pharm. Res., Keystone Symposia, 5–11 Mar. 1994, Santa Fe, N. Mex., discloses 4-hydroxy-3-(3-phenoxypropyl)-1-benzopyran-2-one as an HIV protease inhibitor.

Structural Biology, 1(1):199–200 (April 1994) discloses that the rat poison warfarin was a useful lead in the search for HIV proteinase inhibitors.

CA 85:78002b (1976) discloses 3-(2,4,6-trihydroxybenzyl)-4-hydroxy-2H-pyran-2-one derivatives as having anti-bacterial activity.

FR, A, 1092278 (Hoffman) (1955) discloses the preparation of coumarin derivatives, such as 3-[1'-phenyl-propene-(1')-yl)-4-hydroxycoumarin.

International Publication No. WO 94/11361, published 26 May 1994, discloses pyran-2-ones and 5,6-dihydroxypyran-2-ones as retroviral protease inhibitors.

International Publication No. WO 94/18188, published 18 Aug. 1994, discloses 4-hydroxy-benzopyran-2-ones and 4-hydroxy-cycloalkyl[b]pyran-2-ones as retroviral protease inhibitors.

The following references were cited against the immediate parent application as disclosing the state of the art:

U.S. Pat. No. 3,651,091 (Boschetti, et al.); U.S. Pat. No. 4,262,013 (Mistui, et al.); U.S. Pat. No. 4,900,754 (Regan, et al.); U.S. Pat. No. 5,294,724 (Jendralla, et al.); Australian Patent Specification 219,371 (Enders, et al.); Canadian Patent No. 1,171,424 (Willard, et al.); British Patent Specification 836,740 (Bayer); European Patent Application 0 024 348 (Willard, et al.); European Patent Application 0 588 137 (Fischer, et al.); French Patent No. 1,276,654 (Molho) (cited above); and International Publication No. WO 94/1136 (Thaisrivongs, et al.) (cited above).

"Collaborative Structure-Based Design of Small Organic Molecules as Inhibitors of HIV Proteases," Keystone Symposia, Santa Fe, N. Mex. (5–11 Mar. 1994), discloses the crystallographic complexes of HIV-1 and HIV-2 protease with compounds, such as 3-(α-ethylbenzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one.

"Discovery and Properties of Small Organic Molecules Inhibiting HIV-1 Protease," Keystone Symposia, Santa Fe, N. Mex. (5–11 Mar. 1994), discloses an assay for determining inhibitory activity of compounds, such as 3-(α-ethylbenzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one.

"Structure-based Design of Non-peptide HIV Protease Inhibitors," 35th Annual Buffalo Medicinal Chemistry Symposium, Buffalo, N.Y. (22–25 May 1994), discloses compounds, such as 3-(α-ethylbenzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one, as potential anti-HIV therapeutic agents.

In Hruby et. al. (J. Org. Chem., 58 (26):7567 (1993), a description of the copper catalyzed addition of an aryl Grignard to an unsaturated chiral amide, 3-(2-butenoyl)-4-phenyl-2-oxazolidinone, is given. In Evans et. al. (J. Am. Chem. Soc., 112:8215 (1990), the reaction between a chiral amide and 2-methoxy-2-methyl-1,3-dioxoline is described. The preparation of 2-methoxy-2-methyl-1,3-dioxoline is found in Santry et. al. (J. Am. Chem. Soc., 110 (9):2910 (1988). For references on the reaction between an ester enolate and a ketone, refer to Dongala et. al., Tetrahedron Letters, 4983 (1973), and Mitsui et. al., Tetrahedron, 23:4271 (1967). For references on the reaction between an amide enolate and a ketone, refer to Viteva et. al., Tetrahedron 50:7193 (1994); Oare et. al., J. Org. Chem. 55:132 (1990); Hullot et. al., Can. J. Chem. 55:266 (1977); Woodbury et. al., J. Org. Chem. 42:1688 (1977); Stefanovsky et. al., Tetrahedron 42:5355 (1986); and Mathew et. al., U.S. Pat. No. 5,284,975.

G. Carganico, P. Cozzi, G. Orsini, J. Med. Chem., 26:1767–1769 (1983), discloses synthesized compounds with a methyl and a hydroxyl group at the 4-position of the dihydropyrone ring and no substitution at the 3-position. The compounds of the present invention have a ketone at the 4-position (which may be in enol form) and substitution at the 3-position.

D. T. Witiak et al., J. Med. Chem., 31:1437–1445 (1988), discloses benzopyran-2-ones with a hydroxy group at the 3-position. The compounds of the present invention have alkyl substitution at that position.

B. Tait, Winter Conference on Bioorganic Medicinal Chemistry, 29 Jan.–2 Feb. 1995, Steamboat Springs, Colorado, disclosed a dihydropyrone having a phenyl group and a pentyl group at the 6-position and a —S—CH_2—CH_2-phenyl group at the 3-position in the HIV protease area.

J. V. N. Vara Prasad, et al., J. Med. Chem., 38:898–905 (1995), discloses 4-hydroxy-6-phenyl-2-oxo-2H-pyran-3-yl)thiomethanes, such as (+)-3-[cyclopentyl (cyclopentylthio)methyl]-4-hydroxy-6-phenyl-2H-pyran-2-one, as HIV-1 protease inhibitors.

SUMMARY OF THE INVENTION

The present invention provides:

A compound of the formula I

wherein R_1 is H—;

wherein R_2 is

a) C_3–C_5 alkyl,

b) phenyl-$(CH_2)_2$—,

c) het—SO_2NH—$(CH_2)_2$—,

d) cyclopropyl-$(CH_2)_2$—,

e) F-phenyl-$(CH_2)_2$—,

f) het—SO_2NH-phenyl-, or

g) F_3C—$(CH_2)_2$—;

or wherein R_1 and R_2 taken together are a double bond;

wherein R_3 is the moiety of formula X

wherein R_4 is

a) phenyl,

b) het,

c) cyclopropyl,

d) H_3C—$[O(CH_2)_2]_2$—,

e) het—SO_2NH—,

f) Br—,

g) N_3—, or
h) $HO_3S(CH_2)_2$—$N(CH_3)$—C(O)—$(CH_2)_6$—C(O)—NH—;

wherein R_5 is —H;

wherein R_6 is
a) R_4—$(CH_2)_n$—$CH(R_8)$—,
b) H_3C—$[O(CH_2)_2]_2$—CH_2—,
c) C_3–C_5 alkyl,
d) phenyl-$(CH_2)_2$—,
e) het—SO_2NH—$(CH_2)_2$—,
f) $(HOCH_2)_3C$—NH—C(O)—NH—$(CH_2)_3$—,
g) $(HO_2C)(H_2N)CH$—$(CH_2)_2$—C(O)—NH—$(CH_2)_3$—,
h) piperazin-1-yl-C(O)—NH—$(CH_2)_3$,
i) $HO_3S(CH_2)_2$—$N(CH_3)$—C(O)—$(CH_2)_6$—C(O)—NH—$(CH_2)_3$—,
j) cyclopropyl-$(CH_2)_2$—,
k) F-phenyl-$(CH_2)_2$—,
l) het—SO_2NH-phenyl, or
m) F_3C—$(CH_2)_2$—;

wherein n is zero (0), one (1) or two (2);

wherein R_7 is
a) cyclopropyl,
b) CH_3—CH_2—, or
c) t-butyl;

wherein R_8 is
a) —CH_2—CH_3, or
b) —CH_2-cyclopropyl;

wherein R_9 is
a) —$NR_{12}SO_2$—het,
b) —$NR_{12}SO_2$-phenyl substituted by zero (0) or one (1) R_{11},
c) —CH_2—SO_2-phenyl substituted by zero (0) or one (1) R_{11}, or
d) —CH_2—SO_2—het;

wherein het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one (1) to three (3) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; substituted by zero (0) or one (1) R_{10};

wherein R_{10} is
a) —CH_3,
b) —CN,
c) —OH,
d) —$C(O)OC_2H_5$,
e) —CF_3,
f) —NH_2, or
g) —C(O)—NH_2;

wherein R_{11} is
a) —CN,
b) —F,
c) —OH, or
d) —NO_2;

wherein R_{12} is
a) —H, or
b) —CH_3;

or a pharmaceutically acceptable salt thereof.

The present invention more particularly provides:

A compound of the formula I

wherein R_1 is H—;

wherein R_2 is
a) C_3–C_5 alkyl,
b) phenyl-$(CH_2)_2$—, or
c) het—SO_2NH—$(CH_2)_2$—;

or wherein R_1 and R_2 taken together are a double bond;

wherein R_3 is the moiety of formula X

wherein R_4 is
a) phenyl,
b) het,
c) cyclopropyl,
d) H_3C—$[O(CH_2)_2]_2$—,
e) het—SO_2NH—,
f) Br—,
g) N_3—, or
h) $HO_3S(CH_2)_2$—$N(CH_3)$—C(O)—$(CH_2)_6$—C(O)—NH—;

wherein R_5 is —H;

wherein R_6 is
a) R_4—$(CH_2)_n$—$CH(R_8)$—,
b) H_3C—$[O(CH_2)_2]_2$—CH_2—,
c) C_3–C_5 alkyl,
d) phenyl-$(CH_2)_2$—,
e) het—SO_2NH—$(CH_2)_2$—,
f) $(HOCH_2)_3C$—NH—C(O)—NH—$(CH_2)_3$—,
g) $(HO_2C)(H_2N)CH$—$(CH_2)_2$—C(O)—NH—$(CH_2)_3$—,
h) piperazin-1-yl-C(O)—NH—$(CH_2)_3$, or
i) $HO_3S(CH_2)_2$—$N(CH_3)$—C(O)—$(CH_2)_6$—C(O)—NH—$(CH_2)_3$—;

wherein n is zero (0), one (1) or two (2);

wherein R_7 is
a) cyclopropyl,
b) CH_3—CH_2—, or
c) t-butyl;

wherein R_8 is
a) —CH_2—CH_3, or
b) —CH_2-cyclopropyl;

wherein R_9 is
a) —$NR_{12}SO_2$—het,
b) —$NR_{12}SO_2$-phenyl substituted by zero (0) or one (1) R_{11},
c) —CH_2—SO_2-phenyl substituted by zero (0) or one (1) R_{11}, or
d) —CH_2—SO_2—het;

wherein het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one (1) to three (3) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; substituted by zero (0) or one (1) R_{10};

wherein R_{10} is
a) —CH_3,
b) —CN,
c) —OH, or
d) —$C(O)OC_2H_5$;

wherein R_{11} is
a) —CN,
b) —F,
c) —OH, or
d) —NO_2;

wherein R_{12} is
a) —H, or
b) —CH_3;

or a pharmaceutically acceptable salt thereof.

The present invention provides for such compounds wherein het is the following, substituted by zero (0) or one (1) R_{10},

a) 2-pyridinyl,
b) imidazol-2-yl,
c) imidazol-4-yl,
d) benzimidazol-2-yl,
e) quinolin-8-yl,
f) quinolin-2-yl,
g) pyrimidin-2-yl,
h) quinazolin-2-yl,
i) purin-6-yl,
j) thiazol-2-yl,
k) thiazol-4-yl,
l) 2-pyrazolyl,
m) 2-pyrazinyl,
n) tetrahydropyran-4-yl, or
o) tetrahydropyran-3-yl.

Also more particularly, the present invention provides for the compound of the formula I

wherein R_1 is H—;
wherein R_2 is
a) $H_3C—(CH_2)_2—$,
b) phenyl-$(CH_2)_2$—,
c) $(CH_3)_2CH—CH_2$, or
d) pentyl;
or wherein R_1 and R_2 taken together are a double bond;
wherein R_3 is the moiety of formula X
wherein R_4 is
a) phenyl,
b) het,
c) cyclopropyl,
d) $H_3C—[O(CH_2)_2]_2—$,
e) het—SO_2NH—,
f) Br—,
g) N_3—, or
h) $HO_3S(CH_2)_2—N(CH_3)—C(O)—(CH_2)_6—C(O)—NH—$;
wherein R_5 is —H;
wherein R_6 is
a) $R_4—(CH_2)_n—CH(R_8)—$,
b) $H_3C—[O(CH_2)_2]_2—CH_2—$,
c) $H_3C—(CH_2)_2—$,
d) phenyl-$(CH_2)_2$—,
e) $(CH_3)_2CH—CH_2$—, or
f) pentyl;
wherein n is zero (0), one (1) or two (2);
wherein R_7 is
a) cyclopropyl, or
b) $CH_3—CH_2$—;
wherein R_8 is
a) —$CH_2—CH_3$, or
b) —CH_2-cyclopropyl;
wherein R_9 is
a) —$NHSO_2$—het, or
b) —$NHSO_2$-phenyl substituted by zero (0) or one (1) R_{11};
wherein het is the following, substituted by zero (0) or one (1) R_{10},
a) 2-pyridinyl,
b) imidazol-2-yl,
c) imidazol-4-yl,
d) quinolin-8-yl,
e) tetrahydropyran-4-yl,
f) tetrahydropyran-3-yl, or
g) benzimidazol-2-yl;
wherein R_{10} is
a) —CH_3;
wherein R_{11} is
a) —CN,
b) —F or
c) —NO_2;
or a pharmaceutically acceptable salt thereof.

Most particularly, the present invention provides for the compound of the formula VI

wherein R_2 is
a) $H_3C—(CH_2)_2$—,
b) phenyl-$(CH_2)_2$—,
c) $(CH_3)_2CH—CH_2$—, or
d) pentyl;
wherein R_3 is the moiety of formula X
wherein R_6 is
a) $H_3C—(CH_2)_2$—,
b) phenyl-$(CH_2)_2$—,
c) $(CH_3)_2CH—CH_2$—, or
d) pentyl;
wherein R_7 is
a) $CH_3—CH_2$—, or
b) cyclopropyl;
wherein R_9 is
a) —$NHSO_2$-phenyl substituted by one (1) R_{11}, or
b) —$NHSO_2$—het;
wherein het is the following, substituted by zero (0) or one (1) R_{10},
a) imidazol-4-yl, or
b) quinolin-8-yl;
wherein R_{10} is —CH_3;
wherein R_{11} is
a) —CN, or
b) —F.

Also, most particularly, the present invention provides for the compound of the formula VII

wherein R_3 is the moiety of formula X
wherein R_4 is
a) phenyl,
b) het,
c) cyclopropyl,
d) $H_3C—[O(CH_2)_2]_2$—,
e) het—SO_2NH—,
f) Br—,
g) N_3—, or
h) $HO_3S(CH_2)_2—N(CH_3)—C(O)—(CH_2)_6—C(O)—NH—$;
wherein R_6 is
a) $R_4—(CH_2)_n—CH(R_8)$—, or
b) $H_3C—[O(CH_2)_2]_2—CH_2$—;
wherein R_7 is cyclopropyl;
wherein R_8 is
a) $CH_2—CH_3$, or
b) —CH_2-cyclopropyl;
wherein R_9 is
a) —$NHSO_2$—het, or
b) —$NHSO_2$-phenyl substituted by one (1) R_{11};
wherein n is zero (0), one (1) or two (2);
wherein het is the following, substituted by zero (0) or one (1) R_{10},
a) imidazol-4-yl,
b) imidazol-2-yl,
c) quinolin-8-yl,

d) tetrahydropyran-3-yl,
e) tetrahydropyran-4-yl,
f) 2-pyridinyl, or
g) benzimidazol-2-yl;

wherein R_{10} is —CH_3;

wherein R_{11} is
a) —NO_2,
b) —F, or
c) —CN;

or a pharmaceutically acceptable salt thereof.

The present invention also provides:

A compound of the formula II

wherein R_{10} and R_{20} taken together are
a) the moiety of formula III, or
b) the moiety of formula IV;

wherein p is four (4);

wherein R_1 is —H;

wherein R_2 is
a) H—,
b) CH_3O—, or
c) CH_3O—$[(CH_2)_2O]_3$—;

wherein R_3 is the moiety of formula V

wherein R_4 is
a) cyclopropyl, or
b) —CH_2—$CH(CH_3)_2$;

wherein R_5 is
a) —NR_9SO_2-phenyl substituted by zero (0) or one (1) R_6,
b) —NR_9SO_2—het,
c) —CH_2—SO_2-phenyl substituted by zero (0) or one (1) R_6, or
d) —CH_2—SO_2—het;

wherein R_6 is
a) —CN,
b) —F,
c) —CH_3,
d) —COOH, or
e) —OH;

wherein het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one (1) to three (3) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; substituted by zero (0), one (1) or two (2) R_7;

wherein R_7 is
a) —CH_3,
b) —CN,
c) —$C(O)OC_2H_5$, or
d) —OH;

wherein R_8 is
a) —H,
b) —$(CH_2)_2$—CH_3,
c) —CH_2-cyclopropyl, or
d) —CH_2-phenyl;

wherein R_9 is
a) —H, or
b) —CH_3;

or a pharmaceutically acceptable salt thereof.

The present invention provides for such compounds wherein het is the following, substituted by zero (0) or one (1) R_7,
a) 2-pyridinyl,
b) imidazol-2-yl,
c) imidazol-4-yl,
d) benzimidazol-2-yl,
e) quinolin-8-yl,
f) quinolin-2-yl,
g) pyrimidin-2-yl,
h) quinazolin-2-yl,
i) purin-6-yl,
j) thiazol-2-yl,
k) thiazol-4-yl,
l) 2-pyrazolyl,
m) 2-pyrazinyl,
n) tetrahydropyran-4-yl, or
o) tetrahydropyran-3-yl.

More particularly, the present invention provides for the compound of the formula II

wherein R_{10} and R_{20} taken together are
a) the moiety of formula III, or
b) the moiety of formula IV;

wherein p is four (4);

wherein R_1 is —H;

wherein R_2 is
a) CH_3O—, or
b) $CH_3O[(CH_2)_2O]_3$—;

wherein R_3 is the moiety of formula V

wherein R_4 is
a) cyclopropyl, or
b) —CH_2—$CH(CH_3)_2$;

wherein R_5 is
a) —NR_9SO_2-phenyl substituted by zero (0) or one (1) R_6,
b) —NR_9SO_2—het,
c) —CH_2—SO_2-phenyl substituted by zero (0) or one (1) R_6, or
d) —CH_2—SO_2—het;

wherein R_6 is
a) —CN,
b) —F,
c) —CH_3, or
d) —COOH;

wherein het is the following, substituted by zero (0) or one (1) R_7,
a) imidazol-4-yl,
b) quinolin-8-yl,
c) 2-pyridinyl, or
d) 4-pyridinyl;

wherein R_7 is —CH_3;

wherein R_8 is
a) —H, or
b) —$(CH_2)_2$—CH_3;

wherein R_9 is
a) —H, or
b) —CH_3;

or a pharmaceutically acceptable salt thereof.

Most particularly, the present invention provides for the compound of the formula VIII

wherein R_3 is the moiety of formula V

wherein R_4 is
a) cyclopropyl,
b) —CH_2—$CH(CH_3)_2$;

wherein R_5 is
a) —NR_9SO_2-phenyl substituted by zero (0) or one (1) R_6,

b) —NR_9SO_2—het, or
c) —CH_2—SO_2-phenyl;

wherein R_6 is
a) —CN, or
b) —F;

wherein het is the following, substituted by zero (0) or one (1) R_7,
a) 2-pyridinyl,
b) 4-pyridinyl, or
c) imidazol-4-yl;

wherein R_7 is —CH_3;

wherein R_8 is
a) —H, or
b) —$(CH_2)_2$—CH_3;

wherein R_9 is
a) —H, or
b) —CH_3;

or a pharmaceutically acceptable salt thereof.

Also, most particularly, the present invention provides for the compound of the formula IX

wherein R_1 is H—:

wherein R_2 is
a) CH_3O—, or
b) CH_3O—$[(CH_2)_2O]_3$—;

wherein R_3 is the moiety of formula V

wherein R_4 is cyclopropyl;

wherein R_5 is —$NHSO_2$—het;

wherein het is the following, substituted by zero (0) or one (1) R_7,
a) imidazol-4-yl,
b) 2-pyridinyl, or
c) quinolin-8-yl;

wherein R_7 is —CH_3.

The present invention also provides for the compound of the formula VI

wherein R_2 is
a) H_3C—CH_2—,
b) H_3C—$(CH_2)_2$—,
c) cyclopropyl-$(CH_2)_2$—,
d) F-phenyl-$(CH_2)_2$—,
e) het—SO_2NH-phenyl-,
f) $(H_3C)_2HC$—CH_2,
g) phenyl-$(CH_2)_2$—, or
h) F_3C—$(CH_2)_2$—;

wherein R_3 is the moiety of formula X

wherein R_6 is
a) H_3C—CH_2—,
b) H_3C—$(CH_2)_2$—,
c) cyclopropyl-$(CH_2)_2$—,
d) F-phenyl-$(CH_2)_2$—,
e) het—SO_2NH-phenyl,
f) $(H_3C)_2HC$—CH_2,
g) phenyl-$(CH_2)_2$—, or
h) F_3C—$(CH_2)_2$—;

wherein R_7 is
a) H_3C—CH_2—,
b) t-butyl, or
c) cyclopropyl

wherein R_9 is
a) —$NHSO_2$—het, or
b) —$NHSO_2$-phenyl substituted by one (1) R_{11};

wherein het is the following, substituted by zero (0) or one (1) R_{10},
a) imidazol-4-yl,
b) 2-pyridinyl, or
c) quinolin-8-yl;

wherein R_{10} is,
a) —CH_3,
b) —CN,
c) —CF_3,
d) —NH_2 or
e) —C(O)—NH_2;

wherein R_{11} is CN.

The present invention also provides:

A compound of the formula XI

wherein R_1 is —$(CH_2)_p$—$CH(R_2)$—$(CH_2)_o$—Ar_1;

wherein R_2 is
a) —C_1–C_5 alkyl, or
b) —$(CH_2)_q$-cycloalkyl;

wherein Ar_1 is
a) phenyl substituted by zero (0) or one (1) R_3, or
b) phenyl substituted by -meta-$NHSO_2Ar_2$;

wherein Ar_2 is
a) phenyl substituted by zero (0) or one (1) R_3, or
b) het;

wherein het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one (1) to three (3) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; substituted by zero (0) or one (1) R_4;

wherein R_3 is
a) —CN,
b) —F,
c) —OH, or
d) —NO_2;

wherein R_4 is
a) —CH_3,
b) —CN,
c) —OH,
d) —$C(O)OC_2H_5$,
e) —CF_3, or
f) —NH_2;

wherein n is zero (0) to eight (8), inclusive;

wherein o is zero (0) to three (3), inclusive;

wherein p is zero (0) to three (3), inclusive;

wherein q is zero (0) to three (3), inclusive; or

a pharmaceutically acceptable salt thereof.

More particularly, the present invention provides:

The compound wherein R_1 is —$CH(R_2)$—Ar_1;

wherein R_2 is
a) —CH_2—CH_3, or
b) -t-butyl;

wherein Ar_1 is phenyl substituted by -meta-$NHSO_2Ar_2$;

wherein Ar_2 is 2-pyridinyl substituted by one (1) R_4;

wherein R_4 is
a) —CN, or
b) —CF_3;

wherein n is two (2) to four (4) inclusive.

The present invention also provides:

A process for producing a compound of the formula W-10

wherein R_1 is
a) n-propyl, or
b) phenethyl;

which comprises the steps of:
a) treating a compound of the formula W-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or propylphenethylketone to yield the compound of formula W-10;

The process which further comprises the steps of:

d) treating the compound of formula W-10 with sodium hydride or potassium t-butoxide to obtain a compound of formula W-11

wherein R_1 is

a) n-propyl, or

b) phenethyl;

e) hydrogenating the compound of formula W-11 to obtain the compound of formula W-12

wherein R_1 is as defined above;

f) treating the compound of formula W-12 with a sulfonyl chloride of formula D-7

wherein R_4 is 5-trifluoromethyl-2-pyridinyl, in an organic solvent in the presence of an organic base to obtain a compound of the formula W-13

wherein R_1 is as defined above.

The present invention also provides:

A process for producing a compound of the formula X-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula X-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or propylphenethylketone to yield the compound of formula X-10;

The process which further comprises the steps of:

d) treating the compound of formula X-10 with sodium hydride or potassium t-butoxide to obtain a compound of formula X-11

wherein R_1 is

a) n-propyl, or

b) phenethyl;

e) hydrogenating the compound of formula X-11 to obtain a compound of formula X-12 wherein R_1 is as defined above;

f) treating the compound of formula X-12 with a sulfonyl chloride of formula D-7

wherein R_4 is 5-trifluoromethyl-2-pyridinyl, in an organic solvent in the presence of an organic base to obtain a compound of the formula X-13

wherein R_1 is as defined above.

The present invention also provides:

A process for producing a compound of the formula GGG-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula GGG-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula GGG-10.

The process which further comprises the steps of:

d) treating the compound of formula GGG-10 with sodium hydride or potassium t-butoxide to obtain a compound of formula GGG-11

wherein R_1 is

a) n-propyl, or

b) phenethyl;

e) hydrogenating the compound of formula GGG-11 to obtain a compound of formula GGG-12

wherein R_1 is as defined above;

f) treating the compound of formula GGG-12 with a sulfonyl chloride of formula D-7

wherein R_4 is

a) 5-trifluoromethyl-2-pyridinyl, or

b) 5-cyano-2-pyridinyl, in an organic solvent in the presence of an organic base to obtain a compound of the formula GGG-13A

wherein R_1 is as defined above.

A process for producing a compound of the formula HHH-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula HHH-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula HHH-10.

The process which further comprises the steps of:

d) treating the compound of formula HHH-10 with sodium hydride or potassium t-butoxide to obtain a compound of formula HHH-11

wherein R_1 is

a) n-propyl, or

b) phenethyl;

e) hydrogenating the compound of formula HHH-11 to obtain a compound of formula HHH-12

wherein R_1 is as defined above;

f) treating the compound of formula HHH-12 with a sulfonyl chloride of formula D-7

wherein R_4 is

a) 5-trifluoromethyl-2-pyridinyl, or

b) 5-cyano-2-pyridinyl, in an organic solvent in the presence of an organic base to obtain a compound of the formula HHH-13A

wherein R_1 is as defined above.

A process for producing a compound of the formula III-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula III-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula III-10.

The process which further comprises the steps of:

d) treating the compound of formula III-10 with sodium hydride or potassium t-butoxide to obtain a compound of formula III-11

wherein R_1 is

a) n-propyl, or

b) phenethyl;

e) hydrogenating the compound of formula III-11 to obtain a compound of formula III-12

wherein R_1 is as defined above;

f) treating the compound of formula III-12 with a sulfonyl chloride of formula D-7

wherein R_4 is

a) 5-trifluoromethyl-2-pyridinyl, or

b) 5-cyano-2-pyridinyl, in an organic solvent in the presence of an organic base to obtain a compound of the formula III-13A

wherein R_1 is as defined above.

A process for producing a compound of the formula JJJ-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula JJJ-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula JJJ-10.

The process which further comprises the steps of:

d) treating the compound of formula JJJ-10 with sodium hydride or potassium t-butoxide to obtain a compound of formula JJJ-11

wherein R_1 is

a) n-propyl, or

b) phenethyl;

e) hydrogenating the compound of formula JJJ-11 to obtain a compound of formula JJJ-12

wherein R_1 is as defined above;

f) treating the compound of formula JJJ-12 with a sulfonyl chloride of formula D-7

wherein R_4 is

a) 5-trifluoromethyl-2-pyridinyl, or

b) 5-cyano-2-pyridinyl, in an organic solvent in the presence of an organic base to obtain a compound of the formula JJJ-13A

wherein R_1 is as defined above.

The present invention most preferably provides:

The compound of formula VI wherein R_2 is

a) $H_3C—(CH_2)_2—$, or

b) phenyl-$(CH_2)_2—$;

wherein R_3 is the moiety of formula X;

wherein R_6 is

a) $H_3C—(CH_2)_2—$, or

b) phenyl-$(CH_2)_2—$;

wherein R_7 is

a) $H_3C—CH_2—$, or

b) t-butyl;

wherein R_9 is $—NHSO_2—$het;

wherein het is the following, substituted by one (1) R_{10},

a) imidazol-4-yl, or

b) 2-pyridinyl;

wherein R_{10} is,

a) $—CH_3$,

b) —CN, or

c) $—CF_3$.

The compounds of the present invention are named according to the IUPAC or CAS nomenclature system.

The carbon atoms content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i–C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_1–C_3 alkyl refers to alkyl of one to three carbon atoms, inclusive, or methyl, ethyl, propyl, and isopropyl, straight and branched forms thereof.

Also, the carbon atom content of various hydrocarbon-containing moieties of the present invention is indicated by a subscripted integer representing the number of carbon and hydrogen atoms in the moiety, e.g., "C_nH_{2n}" indicates a moiety of the integer "n" carbon atoms, inclusive, and the integer "2n" hydrogen atoms, inclusive. Thus, for example, "C_nH_{2n}" wherein n is one to three carbon atoms, inclusive, and two to six hydrogen atoms, inclusive, or methyl, ethyl, propyl and isopropyl, and all isomeric, straight and branched forms thereof.

Examples of alkyl of one to nine carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and nonyl, and all isomeric forms thereof and straight and branched forms thereof.

Examples of alkenyl of one to five carbon atoms, inclusive, are ethenyl, propenyl, butenyl, pentenyl, all isomeric forms thereof, and straight and branched forms thereof.

By "halo" is meant the typical halogen atoms, such as fluorine, chlorine, bromine, and iodine.

The compounds of formula I and II of the present invention inhibit retroviral proteinases and thus inhibit the replication of the virus. They are useful for treating patients infected with human immunodeficiency virus (HIV) which results in acquired immunodeficiency syndrome (AIDS) and related diseases.

More particularly, the compounds of the present invention are useful as novel human retroviral protease inhibitors. Therefore, the compounds inhibit retroviral proteases and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases.

The capsid and replicative enzymes (i.e. protease, reverse transcriptase, integrase) of retroviruses are translated from the viral gag and pol genes as polyproteins that are further processed by the viral protease (PR) to the mature proteins found in the viral capsid and necessary for viral functions and replication. If the PR is absent or nonfunctional, the virus cannot replicate. The retroviral PR, such as HIV-1 PR, has been found to be an aspartic protease with active site characteristics similar to those exhibited by the more complex aspartic protease, renin.

The term human retrovirus (HRV) includes human immunodeficiency virus type I, human immunodeficiency virus type II, or strains thereof, as well as human T cell leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

Patients to be treated would be those individuals: 1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) in the case of HIV, having either an asymptomatic HIV infection or a symp-

tomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm^3 in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the compound used according to this invention in the patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

More specifically, an example of one such human retrovirus is the human immunodeficiency virus (HIV, also known as HTLV-III or LAV) which has been recognized as the causative agent in human acquired immunodeficiency syndrome (AIDS), P. Duesberg, Proc. Natl. Acad. Sci. USA, 86:755 (1989). HIV contains a retro viral encoded protease, HIV-I protease, that cleaves the fusion polypeptides into the functional proteins of the mature viral particle, E. P. Lillehoj, et al., J. Virology, 62:3053 (1988); C. Debuck, et al., Proc. Natl. Acad. Sci., 84:8903 (1987). This enzyme, HIV-I protease, has been classified as an aspartyl protease and has a demonstrated homology to other aspartyl proteases such as renin, L. H. Pearl, et al., Nature 329:351 (1987); I. Katoh, et al., Nature 329:654 (1987). Inhibition of HIV-I protease blocks the replication of HIV and thus is useful in the treatment of human AIDS, E. D. Clerq, J. Med. Chem. 29:1561 (1986). Inhibitors of HIV-I protease are useful in the treatment of HIV-infected individuals who are asymptomatic or symptomatic of AIDS.

Pepstatin A, a general inhibitor of aspartyl proteases, has been disclosed as an inhibitor of HIV-I protease, S. Seelmeier, et al., Proc. Natl. Acad. Sci. USA, 85:6612 (1986). Other substrate derived inhibitors containing reduced bond isosteres or statine at the scissle position have also been disclosed, M. L. Moore, et al., Biochem. Biophys, Res. Commun. 159:420 (1989); S. Billich, et al., J. Biol. Chem. 263:17905 (1988); Sandoz, D. E. 3812-576-A.

Thus, the compounds of the present invention are useful for treating diseases caused by retroviruses, such as human acquired immunodeficiency disease syndrome (AIDS).

The compounds are also useful for treating non-human animals infected with a retrovirus, such as cats infected with feline leukemia virus. Other viruses that infect cats include, for example, feline infectious peritonitis virus, calicivirus, rabies virus, feline immunodeficiency virus, feline parvovirus (panleukopenia virus), and feline chlamydia. Exact dosages, forms and modes of administration of the compounds of the present invention to non-human animals would be apparent to one of ordinary skill in the art, such as a veterinarian.

The compounds of formula I and II of the present invention are prepared as described in the Charts, Preparations and Examples below, or are prepared by methods analogous thereto, which are readily known and available to one of ordinary skill in the art of organic synthesis.

CHART A

Nitration of the cyclopropylphenyl ketone of formula A-1, which is commercially available, with fuming nitric acid at −40° C. produces a ca. 2:1 mixture of isomers. The desired m-nitro compound of formula A-2 is easily separated from the crude mixture by recrystallization from methanol. Catalytic hydrogenation of the cyclopropyl-(3-nitrophenyl) methanone of formula A-2 with 10% platinum on carbon in methanol gives the aniline of formula A-3. The aniline is then coupled with benzenesulfonyl chloride using pyridine in methylene chloride to give the sulfonamide derivative of formula A-4. Reduction of the ketone with sodium borohydride in tetrahydrofuran and ethanol then produces the carbinol of formula A-5.

The dianion of the cyclooctylpyranone of formula A-6, prepared as described in Chart B, is formed using lithium diisopropyl amide in tetrahydrofuran at 0° C., and then alkylated with iodopropane to give the 10-propylcyclooctylpyranone of formula A-7. The cyclooctylpyranone of formula A-7 and the carbinol of the formula A-5 are then coupled using p-toluenesulfonic acid in methylene chloride to give the sulfonamide derivative of formula A-8.

CHART B

The commercially available amine of the formula B-1 is protected using benzyl chloroformate and sodium bicarbonate in THF/water solution to give the compound of formula B-2. The aldehyde of formula B-2 is then reacted with a Grignard reagent to give the secondary alcohol of formula B-3, wherein, e.g., R_1 is isobutyl. The known cyclooctylpyranone of formula B-4 is prepared by acylation of the trimethylsilyl enol ether of cyclooctanone with malonyl dichloride as described in R. Effenberger, T. Ziegler, K.-H. Schonwalder, T. Kesmarszky, B. Bauer Chem. Ber. 119:3394–3404 (1986). The alcohol of formula B-3 is then used to alkylate the cyclooctylpyranone of formula B-4 in refluxing toluene and p-toluenesulfonic acid to obtain the compound of the formula B-5, wherein, e.g., R_1 is isobutyl. At this point, the enantiomers of formula B-5 are separated using a chiral HPLC column. The benzyloxy protecting group is then cleaved using 10% Pd/C in cyclohexene to give the amine of formula B-6, wherein, e.g., R_1 is isobutyl, which is reacted with aryl sulfonyl chlorides to give the compounds of the formula B-7, wherein, e.g., R_1 is isobutyl and R_2 is 1-methylimidazole.

CHART C

3-Bromobenzyl alcohol of formula C-1, which is commercially available, in tetrahydrofuran is treated with methyllithium, n-butyllithium and cyclopropanecarboxaldehyde in sequence at −78° C. The resulting solution is gradually warmed to room temperature and then heated at reflux affording the alcohol of formula C-2. The resulting alcohol, in dichloromethane, in the presence of molecular sieves, is treated with 4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[b]pyran-2-one of formula C-8, prepared as described in Chart B, and p-toluenesulfonic acid. The solution is heated at reflux to afford the alcohol of formula C-3. The benzyl alcohol is treated with carbon tetrabromide and triphenylphosphine in dichloromethane at 0° C. to afford compounds of formula C-4 and C-5 as an inseparable mixture after an aqueous brine workup. The mixture is then treated with any thiol (e.g., thiophenol) and an organic base and heated at reflux to afford sulfides of the formula C-6. Finally treatment of the compounds of the formula C-6 with oxone in a mixture of tetrahydrofuran, methanol and water gives sulfones of formula C-7.

CHART D

This chart describes a generic procedure for the preparation of C-3α branched 5,6-dihydropyrones via aluminum chloride ($AlCl_3$) mediated condensation with 3-nitrobenzaldehyde. Thus, the $AlCl_3$ catalyzed reaction of the compound of formula D-1, prepared as described below in the Preparations, (e.g., wherein R_1 is phenethyl or propyl; R_2 is phenethyl or propyl) with 3-nitrobenzaldehyde

(formula D-2), which is commercially available, provides compounds of formula D-3 (e.g., wherein R_1 is phenethyl or propyl; R_2 is phenethyl or propyl). Subsequent reaction with trialkyl aluminums or Grignard reagents in the presence of cuprous bromide-dimethylsulfide complex (CuBr—Me_2S) provides compounds of formula D-4 (e.g., wherein R_1 is phenethyl or propyl; R_2 is phenethyl or propyl; R_3 is ethyl or cyclopropyl). Transfer hydrogenation with Pd/C and ammonium formate provides compounds of formula D-5 (e.g., wherein R_1 is phenethyl or propyl; R_2 is phenethyl or propyl; R_3 is ethyl or cyclopropyl). Treatment of the compound of formula D-5 with sulfonyl chlorides of formula D-7, wherein R_4 is defined below, and pyridine in methylene chloride (CH_2Cl_2) provides compounds of formula D-6 (e.g., wherein R_1 is phenethyl or propyl; R_2 is phenethyl or propyl; R_3 is ethyl or cyclopropyl; R_4 is 4-cyanophenyl, 4-fluorophenyl, 1-methylimidazol-4-yl, quinolin-8-yl, 2-pyridyl, 4-cyano-2-pyridyl, quinolin-2-yl, 2-hydroxyphenyl, 2-pyrimidyl, 2-quinazoline, 7H-purin-6-yl, 1H-imidazol-2-yl, 1H-benzimidazol-2-yl or thiazol-2-yl).

CHART E

Treatment of commercially available 4-hydroxy-6-methyl-2-pyrone of formula E-1 with three equivalents of lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoramide is followed by bromomethylcyclopropane to afford the compound of formula E-2. Reaction between the compound of formula E-2 and the compound of formula F-5, prepared as described in Chart F, in benzene with p-toluenesulfonic acid catalyst in the presence of molecular sieves affords the compound of formula E-3. Hydrogenolysis of the compound of formula E-3 in methanol with hydrogen and palladium on charcoal gives the free amine of formula E-4. Treatment of the compound of formula E-4 with two equivalents of pyridine in dichloromethane followed by one equivalent of 4-fluorobenzenesulfonyl chloride gives the compound of formula E-5 (wherein, e.g., R is 4-fluorophenyl) which is the compound: N-(3-{cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-4-fluorobenzenesulfonamide.

Under similar conditions, compounds of general formula E-5 are obtained by reacting amine E-4 with alkyl, aryl and heteroaryl sulfonyl chlorides in the presence of pyridine to give compounds of formula E-5 wherein R is alkyl, aryl or heteroaryl. Also, for example, the enantiomers of the compound of formula E-9 are separated chromatographically by chiral HPLC to give compounds of formula E-10 and E-11. Additional final compounds of the present invention of formula E-6, E-7, E-8, and E-12–E-16 are prepared using similar conditions.

CHART F

Nitration of commercially available cyclopropyl phenyl ketone of formula F-1 with fuming nitric acid affords the compound of formula F-2. Reduction of the compound of formula F-2 in methanol with hydrogen catalyzed by platinum on carbon gives the amine of formula F-3. The compound of formula F-3 is treated with benzylchloroformate and diisopropylethylamine in dichloromethane to give the compound of formula F-4. Reduction of the compound of formula F-4 with sodium borohydride in tetrahydrofuran and ethanol gives the compound of formula F-5.

CHART G

The dianion of commercially available 4-hydroxy-6-methyl-2-pyrone of formula G-0 is generated by deprotonation with two equivalents of lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoramide. Alkylation with 2-(2-methoxy-ethoxy)-ethyl iodide, which is prepared from the commercially available alcohol by standard procedures, gives the compound of formula G-1. Reaction between the compound of formula G-1 and meta-benzyloxycarbonylaminophenyl cyclopropyl carbinol, the compound of formula F-5, prepared as described in Chart F, in dichloromethane with p-toluenesulfonic acid catalyst in the presence of molecular sieves gives the compound of formula G-2. Hydrogenolysis of the compound of formula G-2 in ethanol with hydrogen and palladium on charcoal gives the free amine of formula G-3. Treatment of the free amine of formula G-3 with two equivalents of pyridine in dichloromethane followed by one equivalent of 1-methylimidazole-4-sulfonyl chloride gives the compound of formula G-4, which is the compound: N-(3-{cyclopropyl-[4-hydroxy-6-(3-{2-methoxy-ethoxy}-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide.

CHART H

Reaction between commercially available 4-hydroxy-6-methyl-2-pyrone of formula H-0 and meta-benzyloxycarbonylaminophenyl cyclopropyl carbinol, the title compound of formula F-5, prepared as described in Chart F, in dichloromethane with p-toluenesulfonic acid catalyst in the presence of molecular sieves gives the compound of formula H-1. Alkylation of trianion of the compound of formula H-1 generated from three equivalents of lithium diisopropylamide in tetrahydrofuran with ethyl bromide affords the compound of formula H-2. Treatment of the compound of formula H-2 with lithium diisopropylamide in tetrahydrofuran and 2-(2-methoxy-ethoxy)-ethyl iodide gives the compound of formula H-3. Hydrogenolysis of the compound of formula H-3 in ethanol with hydrogen and palladium on charcoal gives the free amine of formula H-4. Treatment of the free amine of formula H-4 with two equivalents of pyridine in dichloromethane followed by one equivalent of 1-methylimidazole-4-sulfonyl chloride gives the compound of formula H-5, which is the compound: N-(3-{cyclopropyl-[6-(1-ethyl-3-{2-methoxy-ethoxy}-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide. Under similar conditions, compounds of the present invention are obtained by reacting the amine of formula H-4 with alkyl, aryl and heteroaryl sulfonyl chlorides in the presence of pyridine to give additional sulfonamides of formula H-5.

CHART I

Treatment of the compound of formula H-2, prepared as described in Chart H, with three equivalents of lithium diisopropylamide in tetrahydrofuran and ethylene oxide gives the compound of formula I-1. Reaction of the compound of formula I-1 with triphenylphosphine and carbon tetrabromide in tetrahydrofuran gives the compound of formula I-2. Treatment of the compound of formula I-2 with sodium azide in aqueous ethanol gives the compound of formula I-3. Reaction of the compound of formula I-3 with hydrogen and palladium on charcoal in ethanol gives the compound of formula I-4. Treatment of the compound of formula I-4 with diisopropylethylamine in dichloromethane followed by 1-methylimidazole-4-sulfonyl chloride gives the compound of formula I-5. Reaction of the compound of formula I-5 with ammonia in methanol gives the compound of formula I-6, which is the compound: N-(3-{cyclopropyl-

[6-(1-ethyl-3-{1-methyl-1H-imidazole-4-sulfonylamino}-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide.

CHART J

Hydrogenolysis of the compound of formula I-1, prepared as described in Chart I, in ethanol with hydrogen and palladium on charcoal gives the compound of formula J-1. Treatment of the compound of formula J-1 with triphenylphosphine and carbon tetrabromide in tetrahydrofuran gives the compound of formula J-2. Reaction of the compound of formula J-2 with pyridine in dichloromethane followed by 1-methylimidazole-4-sulfonyl chloride gives the compound of formula J-3, which is the compound: N-(3-{[6-(3-bromo-1-ethyl-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-cyclopropyl-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide. Treatment of the compound of formula J-3 with sodium azide in aqueous ethanol gives the compound of formula J-4, which is the compound: N-(3-{([6-(3-azido-1-ethyl-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-cyclopropyl-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide. Reaction of the compound of formula J-4 with hydrogen and palladium on charcoal in ethanol gives the compound of formula J-5. Treatment of the compound of formula J-5 with the triethylamine salt of suleptanic acid (Anderson, B. D.; Conradi, R. A; Knuth, K. E.; J. Pharm. Sci. 74:365 (1985)) and 1,3-diisopropylcarbodiimide gives the compound of formula J-6, which is the compound: N-(3-{cyclopropyl-[6-(1-ethyl-3-{N-[8-(methyl-{2-sulfoethyl}-amino)-1,8-dioxooctyl]amino-propyl})-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide, sodium salt.

CHART K

The preparation of the compound of formula K-8, which is the compound: N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide is shown in Chart K. Reduction of commercially available tetrahydropyran-4-carboxylic acid of formula K-1 with borane in tetrahydrofuran provides the compound of formula K-2. The compound of formula K-2 is treated with p-toluenesulfonyl chloride to afford the corresponding tosylate of formula K-3, which is converted to the iodide of formula K-4 by treatment with potassium iodide in refluxing acetone. Alkylation of the dianion of commercially available 4-hydroxy-6-methyl-2-pyrone of formula K-10 with ethyl bromide in tetrahydrofuran and hexamethylphosphoric triamide gives the propyl derivative of formula K-9. The compound of formula K-4 is used to alkylate the compound of formula K-9 at the 6α position, giving the compound of formula K-5. The compound of formula K-5 is further alkylated at the 3 position, using carbinol of formula F-5, prepared as described in Chart F, giving the compound of formula K-6. Removal of the benzyloxycarbonyl protecting group is accomplished using catalytic transfer hydrogenation, giving the amine of formula K-7. Treatment of the amine of formula K-7 with 1-methylimidazole-4-sulfonyl chloride in the presence of pyridine provides the compound of formula K-8.

CHART L

As shown in Chart L, the dianion of commercially available 4-hydroxy-6-methyl-2-pyrone of formula L-1 is generated by deprotonation with two equivalents of lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoramide. Alkylation with benzyl bromide gives the compound of formula L-2, which is then treated with two equivalents of lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoramide, followed by ethyl iodide to give the compound of formula L-3. Reaction between the compound of formula L-2 and the compound of formula F-5, prepared as described in Chart F, in benzene with p-toluenesulfonic acid catalyst in the presence of molecular sieves affords the compound of formula L-4, which is 3-[(3-benzyloxycarbonylaminophenyl)-cyclopropyl-methyl]-6-(1-ethylphenethyl)-4-hydroxy-2H-pyran-2-one. Hydrogenolysis of the compound of formula L-4 in methanol using catalytic palladium on charcoal and ammonium formate or hydrogen gas gives the free amine of formula L-5, which is 3-[(3-aminophenyl)-cyclopropyl-methyl]-6-(1-ethylphenethyl)-4-hydroxy-2H-pyran-2-one. Reacting the compound of formula L-5 and the appropriate sulfonyl chloride gives the final compounds of the present invention.

CHART M

As shown in Chart M, commercially available triethylene glycol monomethyl ether is treated with p-toluenesulfonyl chloride and pyridine to provide the tosylate of formula M-2, which is then used to alkylate commercially available 2,4-dihydroxyacetophenone to give the compound of formula M-3. Condensation with diethyl carbonate yields the compound of formula M-4. Ring closure of the compound of formula M-4 to the compound of formula M-5 is accomplished by refluxing in acetic acid. The compound of formula M-5 is alkylated at the 3-position using the carbinol of formula F-5, prepared as described in Chart F, and catalytic p-toluenesulfonic acid to give the compound of formula M-6. Removal of the benzyloxycarbonyl protecting group is accomplished using catalytic transfer hydrogenation, giving the amine of formula M-7. Treatment of the amine with 1-methylimidazole-4-sulfonyl chloride in the presence of pyridine provides the final compound of formula M-8, which is N-(3-{Cyclopropyl-[7-(2-(2-(2-methoxyethoxy)-ethoxy)ethoxy)-4-hydroxycoumarin-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide.

CHART N

Nitration of cyclopropylphenyl ketone of formula N-1, which is commercially available, with fuming nitric acid at −40° C. produces a ca. 2:1 mixture of isomers. The desired meta-nitro compound of formula N-2 is easily separated from the crude mixture by recrystallization from methanol. Catalytic hydrogenation of cyclopropyl-(3-nitrophenyl) methanone of formula N-2 with 10% platinum on carbon in methanol at 0° C. provides the aniline of formula N-3. The product is isolated by filtration and concentration. The amino group is then protected using benzyl chloroformate and diisopropylethylamine in methylene chloride to give the ketone of formula N-4. The ketone is then reduced with sodium borohydride in 5:1 THF and ethanol to give the alcohol of formula N-5.

The compound of formula N-5 is then used to alkylate 4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[b]pyran-2-one, which is prepared as described in R. Effenberger, T. Ziegler, K.-H. Schönzoalder, T. Kesmarsky, B. Bauer, Chem. Ber. 119:3394–3404 (1986), to give the compound of formula N-6. The preferred conditions for this alkylation reaction are p-toluene-sulfonic acid in refluxing methylene chloride with a Soxhlet extractor containing molecular sieves. Finally, the compound of formula N-7 is obtained by

cleaving the benzyl protective group in a transfer hydrogenation. Best results for this reactions are achieved with 10% Pd/C in neat cyclohexene.

CHART O

Treatment of the amine of formula O-1, prepared as described in Chart N, with sulfonyl chlorides and a base such as pyridine in dichloromethane gives the sulfonamides of formula O-2 wherein R_{60} is, for example, 4-nitrophenyl. These sulfonamides are further modified by standard literature procedures as is apparent to those of ordinary skill in the art to give sulfonamides of formula O-3 wherein R_{61} is, for example, 4-aminophenyl and other functional groups that are not readily available from readily available sulfonyl chlorides. For example, the nitro group of N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-4-nitro-benzenesulfonamide is reduced by catalytic hydrogenation in ethyl acetate with palladium on carbon to give the amine in 4-amino-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide. Also, the carboxylic acid of 3-[[[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]amino]sulfonyl]-benzoic acid is esterified with methanol and catalytic sulfuric acid to give the methyl ester in 3-[[[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]amino]sulfonyl]-benzoic acid, methyl ester. Sulfonamides of formula O-3 are also obtained from compounds of formula O-2 by further elaboration of reactive functional groups. For example, the amine of 3-amino-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide is reacted with benzoyl chloride and a base such as pyridine to give the benzamide in N-[3-[[[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]amino]sulfonyl]henyl]-benzamide. Using commonly available sulfonyl chlorides, additional compounds of the present invention of formula II, wherein R_{10} and R_{20} is the moiety of formula IV, are prepared.

The sulfonyl chlorides used to make the compounds of the present invention are readily prepared by methods described in the literature by those skilled in the art, as the following examples illustrate: Reaction of a suitable thiol with KHF_2 in water/methanol with chlorine gas gives the sulfonyl fluoride (D. J. Brown, J. A. Hoskins, Aust. J. Chem. 25:2641 (1972)) which is then converted into the desired sulfonyl chloride (T. Norris, J. Chem. Soc., Perkin Trans. 1(11):1378 (Eng.) (1978)). Oxidation of a suitable thiol with chlorine in water with ferric chloride ($FeCl_3$) added gives the desired sulfonyl chloride (G. Pala, Ed. Sci. 13:461 (1958); W. J. Close, J. Amer. Chem. Soc. 82:1132 (1960)). Reaction of the heteroaromatic compound with fuming sulfuric acid gives a heteroaromatic sulfonic acid followed by treatment with phosphorous-oxychloride ($POCl_3$) and phosphorous chloride (PCl_5) gives the desired sulfonyl chloride (V. Georgian, R. J. Harrison, L. L. Skaletzky, J. Org. Chem. 27:4571 (1962)). Reaction of a heteroaromatic compound with manganese dioxide (MnO_2) and sodium sulfite (Na_2SO_3) in water gives the desired sulfonic acid followed by treatment with $POCl_3$ and PCl_5 gives the desired sulfonyl chloride (N. A. Androva, Izvest. 455 (1972); J. O. Morley, J. Chem. Comm. 88 (1976)). Treatment of the appropriate heteroaromatic chloride with sodium sulfate and HCl in water gives the desired sulfonic acid followed by treatment with $POCl_3$ and PCl_5 gives the desired sulfonyl chloride (T. R. Norton, J. Amer. Chem. Soc. 68:1330 (1946)). Treatment of the appropriate hydroxy compound with N,N-dimethylthiocarbonyl chloride (M. S. Newman, F. W. Hetzel, Org. Synth. Coll. Vol. IV:824 (1988); M. S. Newman, H. A. Karnes, J. Org. Chem. 31:3980 (1966)) followed by treatment of the resulting thiol, as described above, gives the desired sulfonyl chloride. Treatment of the appropriately protected thio-heteroaromatic compound with chlorine in acetic acid gives the desired sulfonyl chloride (Can. J. Chem. 55:421 (1977)). Using the literature procedures described above, the heteroaromatic sulfonyl chlorides of the present invention are prepared.

CHART P

The preferred procedure for the preparation of the heteroaryl sulfonamides of formula P-2 is described in Chart P. Sulfonation of the amine of formula P-1, prepared in Chart N, P-1 with various heteroarylsulfonyl chlorides of formula P-3 wherein R is, e.g., 2-pyridyl, 4-pyridyl, 5-cyanopyridin-2-yl, 2-pyrazinyl, 2-pyrimidinyl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl gives the sulfonamides of formula P-2 wherein R is the corresponding substituent.

CHART Q

Generated by sequential deprotonation with sodium hydride and n-butyl lithium in tetrahydrofuran at 0° C., the dianion of commercially available methyl acetoacetate is reacted with ketone of formula Q-1, prepared as described in Chart S (formula S-4). The resulting intermediate hydroxy-ester is cyclized with dilute aqueous hydroxide followed by aqueous hydrochloric acid to give the compound of formula Q-2. The compound of formula Q-2 is condensed with commercially available 3-nitrobenzaldehyde in tetrahydrofuran using aluminum trichloride as a catalyst followed by reaction of the intermediate benzylidene adduct with triethyl aluminum in the presence of copper bromide-dimethyl sulfide to provide the compound of formula Q-3. Catalytic transfer hydrogenation with Pd/C and ammonium formate in methanol affords the compound of formula Q-4. Treatment of the compound of formula Q-4 with the appropriate sulfonyl chloride and pyridine in dichloromethane provides the desired compound of formula Q-5 (wherein, e.g., R_1 is 5-cyano-2-pyridyl or 1-methylimidazol-4-yl).

CHART R

Catalytic hydrogenation of commercially available 3-nitropropiophenone of formula R-1 affords the amine of formula R-2. The amine of formula R-2 is treated with diisopropylethylamine and benzyl bromide to give the compound of formula R-3. The dianion of methyl acetoacetate, generated by treatment of commercially available methyl acetoacetate with sodium hydride and n-butyl lithium in tetrahydrofuran at 0° C., is reacted with the ketone of formula R-3. The intermediate hydroxy-ester is cyclized with dilute aqueous hydroxide followed by aqueous hydrochloric acid to give the compound of formula R-4. The compound of formula R-4 is condensed with 3-nitrobenzaldehyde in tetrahydrofuran using aluminum trichloride as a catalyst followed by reaction of the intermediate benzylidene adduct with triethyl aluminum in the presence of copper bromide-dimethyl sulfide to provide the compound of formula R-5. Catalytic hydrogenation with Pd/C affords the diamine of formula R-6. Treatment of the compound of formula R-6 with the appropriate sulfonyl chloride and pyridine in dichloromethane provides the desired compound of formula R-7 (wherein, e.g., R_1 is 5-cyano-2-pyridyl or 1-methylimidazol-4-yl).

CHART S

Commercially available 4-pentenoic acid of formula S-1 is coupled with N,O-dimethylhydroxylamine using bis(2-oxo-3-oxazolidinyl)phosphinic chloride to afford the amide of formula S-2. The amide of formula S-2 is reacted with 3-butenyl magnesium bromide in tetrahydrofuran to give the ketone of formula S-3. The ketone of formula S-3 is treated with zinc metal, cuprous chloride and diiodomethane to provide the ketone of formula S-4 (also formula Q-1, see Chart Q above).

CHART T

The compound of formula T-2 (also formula D-1) (whose preparation is specifically described in Chart D and Preparation 17 above from commercially available methyl acetoacetate and 1-phenyl-3-hexanone (formula T-1)) is condensed with 3-nitrobenzaldehyde in tetrahydrofuran using aluminum trichloride as a catalyst followed by reaction of the intermediate benzylidene adduct with t-butylCu(CN)ZnI, (the organometallic reagent derived from zinc metal, 2-iodo-2-methyl-propane, copper cyanide and lithium chloride) to provide the compound of formula T-3. (The preparation of the organometallic reagent is further described in the text corresponding to Preparation J above). Catalytic transfer hydrogenation with Pd/C and ammonium formate in methanol affords the compound of formula T-4. Treatment of the compound of formula T-4 with the appropriate sulfonyl chloride and pyridine in dichloromethane provides the desired compound of formula T-5 (wherein, e.g., R_1 is 5-cyano-2-pyridyl or 1-methylimidazol-4-yl).

CHART U

Commercially available 4-fluorohydrocinnamic acid of formula U-1 is coupled with N,O-dimethylhydroxylamine using diethyl cyanophosphonate to provide the amide of formula U-2. Treatment of the amide with n-propylmagnesium chloride yields the ketone of formula U-3. Condensation of the ketone with the dianion of methyl acetoacetate, followed by hydrolysis of the intermediate ester and ring closure, provides the dihydropyrone of formula U-4. Reaction of the dihydropyrone with the aldehyde of formula B-2, prepared as described in Chart B above, in the presence of $AlCl_3$ provides the benzylidene compound of formula U-5; subsequent reaction with Grignard reagents or trialkyl aluminums in the presence of cuprous bromide-dimethyl sulfide complex affords compounds of formula U-6 (wherein, e.g., R_1 is ethyl, tert-butyl, or cyclopropyl). Removal of the benzyloxy-carbonyl (CBZ) protecting group is accomplished using ammonium formate and palladium on charcoal to give the amines of formula U-7 (wherein, e.g., R_1 is ethyl, tert-butyl, or cyclopropyl). Treatment of the amines with sulfonyl chlorides and pyridine in methylene chloride provides the sulfonamides of formula U-8 (wherein, e.g., R_1 is ethyl, tert-butyl, or cyclopropyl and R_2 is alkyl, aryl, or heteroaryl).

CHART V

Commercially available 4-fluorobenzaldehyde of formula V-1 is condensed with acetone, under basic conditions, to provide 1,5-Bis-(4-fluorophenyl)-penta-1,4-dien-3-one of formula V-2. The dienone is reduced with magnesium in methanol to provide the ketone of formula V-3. The ketone of formula V-3 is converted to dihydropyrone products of formula V-8 using chemistry analogous to that described in Chart U for the sequence of reactions from U-3 to U-8.

CHART W

Commercially available trans 2-pentenoic acid of formula W-1 is converted to the corresponding acid chloride using oxalyl chloride in methylene chloride to afford the product of formula W-2. The lithium amide of formula W-3, readily available from the treatment of commercially available (S)-(+)-4-phenyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at −78° C., is treated with the acid chloride of formula W-2, to give the unsaturated amide of formula W-4. Addition of the amide of formula W-4 to a tetrahydrofuran solution containing commercially available CuBr/$(CH_3)_2S$ and 3-[bis(trimethylsilyl)amino]phenylmagnesium chloride at −20° C. affords the compound of formula W-5 upon acid workup (Hruby et al., J. Org. Chem., 58(26):7567 (1993)). Treatment of the aniline of formula W-5 with benzyl bromide and sodium carbonate in a water/methylene chloride mixture at reflux; or, potassium carbonate in refluxing acetonitrile, affords the compound of formula W-6. Treatment of the amide of formula W-6 with $TiCl_4$ followed by an amine base in a solvent such as methylene chloride at below −20° C., preferably at −78° C., then addition of the 2-methoxy-2-methyl-1,3-dioxoline of formula W-7 (prepared as described in Santry et al., J. Am. Chem. Soc., 110(9):2910 (1988)) affords the compound of formula W-8. Brief treatment of the compound of formula W-8 with a protic acid affords the β-ketoamide of formula W-9. Further treatment of the compound of formula W-9 with $TiCl_4$ followed by an amine base, then 4-heptanone or propylphenethylketone, affords the compound of formula W-10 wherein R_1 is n-propyl or phenethyl, respectively. Treatment of the compound of formula W-10 with sodium hydride or preferably potassium t-butoxide, in an ether solvent then affords the pyrone of formula W-11. Hydrogenation of the compound of formula W-11 using, e.g., a Pd on carbon as the catalyst, affords the compound of formula W-12. Finally, treatment of the compound of formula W-12 with a sulfonyl chloride of formula D-7, wherein R_4 is 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula W-13, wherein R_1 is n-propyl or phenethyl (when R_1 is phenethyl, it is a pair of diastereomers).

CHART X

The final (R) enantiomer of formula X-13, wherein R_1 is n-propyl or phenethyl, is prepared according to the procedures of Chart W.

CHART Y

Acetyl chloride of formula Y-1 is added to the lithium amide of formula Y-2 (also X-3), readily available from the treatment of commercially available (R)-(−)-4-phenyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at −78° C., to afford the product of formula Y-3. The compound of formula Y-3 is treated first with $TiCl_4$ in methylene chloride below room temperature, followed by the addition of a tertiary amine base with subsequent addition of the aldehyde of formula Y-4 (aldehyde of the formula Y-4 is readily available from the reaction of commercially available 3-aminobenzaldehyde with benzyl bromide and potassium or sodium carbonate in either acetonitrile or a water/methylene chloride mixture) to yield the compound of formula Y-5. Addition of the amide of formula Y-5 to a tetrahydrofuran solution containing commercially available CuBr/$(CH_3)_2S$ and ethylmagnesium chloride at −20° C. affords the compound of formula Y-6. Alternatively, the

commercially available compound of formula Y-7 is treated with oxalyl chloride to afford the compound of formula Y-8. The compound of formula Y-8 is then added to a THF solution of the compound of formula Y-2 (also X-3), readily available from the treatment of commercially available (R)-(-)-4-phenyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at -78° C., to yield the compound of formula Y-9. Reduction of the compound of formula Y-9 with iron metal in an alcohol/water mixture then affords the compound of formula Y-10. Treatment of the compound of formula Y-10 with benzyl bromide and potassium or sodium carbonate in either acetonitrile or methylene chloride/water then affords the compound of formula Y-5 which, as described above, is converted to the compound of formula Y-6. The compound of formula Y-6 is converted to final product as described for the conversion of the compound of the formula W-6 to the compound of the formula W-13 (wherein R_1 is propyl or phenethyl) in Chart W.

CHART Z

Preparation of the (3S) amide of formula Z-6 is accomplished in the same manner as outlined in Chart Y above, except using the compound of formula Z-2 (also W-3). The compound of the formula Z-6 is converted to final product as described for the conversion of the compound of formula X-6 to the compound of the formula X-13 (wherein R_1 is propyl or phenethyl) in Chart Z.

CHART AA

Preparation of the 3(S), 6(S) Diastereomers AA-12 and AA-14: Addition of the unsaturated amide of formula AA-1 (also Y-5) to a tetrahydrofuran solution containing commercially available $CuBr/(CH_3)_2S$ and ethylmagnesium chloride at -20° C. affords the compound of formula AA-2 (same as Y-6). Reduction of the compound of formula AA-2 with a metal hydride (sodium borohydride, lithium aluminum hydride) affords the compound of formula AA-3. Oxidation of the compound of formula AA-3 (Swern oxidation) affords the aldehyde of formula AA-4 which is treated with trimethylsilylcyanide to yield the trimethylsilyl protected cyanohydrin of formula AA-5. Alternatively, the compound of formula AA-2 is treated with trimethyl aluminum followed by N-methyl-O-methyl hydroxyl amine to yield the amide of formula AA-6 which is treated with lithium aluminum hydride to yield the aldehyde of formula AA-4. The trimethylsilyl cyanohydrin of formula AA-5 is reacted with a strong base (e.g. n-butyl lithium) followed by the addition of chiral epoxide of formula AA-7 (also BB-12; the synthesis of which is described in Chart BB) to yield the compound of formula AA-8. The compound of formula AA-8 is dissolved in methylene chloride and cooled to -78° C. and $TiCl_4$ is added followed by a tertiary amine base. To that solution is added trimethylorthoformate followed by additional $TiCl_4$ which yields the compound of formula AA-9. Treatment of the compound of formula AA-9 with base followed by trimethylsilyl chloride, then treatment with an oxidizing agent (ozone), followed by treatment with tetrabutyl ammonium fluoride and then either potassium tert. butoxide or sodium hydride in an ether solvent, then affords the compound of formula AA-10. Hydrogenation of the compound of formula AA-10 then affords the compound of formula AA-11. Finally, treatment of the compound of formula AA-11 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula AA-12.

Furthermore, addition of the compound of formula AA-1 to a tetrahydrofuran solution containing commercially available $CuBr/(CH_3)_2S$ and tertiary butylmagnesium chloride at -20° C. affords the compound of formula AA-13. The compound of formula AA-13 is converted to the final product, the compound of formula AA-14, using the chemistry described for the synthesis of AA-12.

CHART BB

Chart BB describes the asymmetric synthesis of epoxides of formula BB-7 and BB-12. Alkylation of 2-methyl-2-propen-1-ol (BB-1) with commercially available benzyl bromide provides the allylic alcohol of formula BB-2 (see Lipshutz, B. H. et al.; Synthesis 1992, 191). Catalytic Sharpless epoxidation using commercially available (+) diethyl L-tartrate provides the epoxy alcohol of formula BB-8 (see: (a) Pfenniger, A.; Synthesis 1986, 89. (b) Johnson, R. A.; Sharpless, K. B. In Catalytic Asymmetric Synthesis; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1, 103.). Alkylation of the compound of formula BB-8 with benzyl bromide (see: Lipshutz, B. H. et al.; Synthesis 1992, 191) gives the compound of formula BB-9. Reaction of the compound of formula BB-9 with commercially available ethylmagnesium bromide affords the tertiary alcohol of formula BB-10 (see: Hanson, R. M. Chem. Rev. 1991, 91, 437). Catalytic hydrogenolysis of the compound of formula BB-10 provides the diol of formula BB-11. The compound of formula BB-11 is converted to the chiral epoxide of formula BB-12 by standard methodology (for a discussion of the conversion of vicinal diols to epoxides see: Mitsunobu, O. In Comprehensive Organic Synthesis; Trost, B. M. Ed.; Pergamon Press: Oxford, 1991; Vol. 6; Chapter 1.1, 1).

In an analogous manner, the epoxide of formula BB-7 is ultimately derived from the epoxy alcohol of formula BB-3, which in turn is prepared by Sharpless epoxidation of allylic alcohol BB-2 using commercially available (-) diethyl D-tartrate.

Alternatively, reaction of the epoxy alcohol of formula BB-8 with commercially available 4-toluenesulfonyl chloride under standard conditions affords the tosylate of formula BB-13. Reaction of the compound of the formula BB-13 with ethylmagnesium bromide under conditions similar to those described for the nucleophilic opening of arenesulfonate derivatives of glycidol (see: Klunder, J. M.; Onami, T.; Sharpless, K. B. J. Org. Chem. 1989, 54, 1295) affords a mixture of the desired epoxide of formula BB-12 and hydroxytosylate of formula BB-14. The hydroxytosylate of formula BB-14 is readily converted to epoxide BB-12 by the action of K_2CO_3 in methanol.

CHART CC

Preparation of the 3(S), 6(R) Diastereomers CC-12 and CC-14: These diastereomers are prepared in a manner identical to that described in Chart AA with the exception that the epoxide of formula CC-7 (same as BB-7) is used.

CHART DD

Preparation of the 3(R), 6(S) Diastereomers DD-12 and DD14: These diastereomers are prepared in a manner identical to that described in Chart AA with the exception that the amide of formula DD-1 (same as Z-5) is used.

CHART EE

Preparation of the 3(R), 6(R) Diastereomers EE-12 and EE-14: These diastereomers are prepared in a manner iden-

tical to that described in Chart DD with the exception that the epoxide of formula EE-7 (same as BB-7) is used.

CHART FF

The lithium amide of formula FF-2, readily available from the treatment of commercially available (S)-(+)-4-phenyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at −78° C., is treated with acetyl chloride of formula FF-1 to give the amide of formula FF-3.Treatment of the compound of formula FF-3 with $TiCl_4$ followed by treatment with a trialkyamine followed by the addition of commercially available trimethylacetaldehyde affords the compound of formula FF-4. Addition of the amide of formula FF-4 to a tetrahydrofuran solution containing commercially available $CuBr/(CH_3)_2S$ and 3-[bis(trimethylsilyl)amino] phenylmagnesium chloride at −20° C. affords the compound of formula FF-5 upon acid workup. Treatment of the aniline of formula FF-5 with benzyl bromide and sodium carbonate in a water/methylene chloride mixture at reflux; or, potassium carbonate in refluxing acetonitrile, affords the compound of formula FF-6.

The lithium amide of formula FF-7, readily available from the treatment of commercially available (S)-(−)-4-benzyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at −78 C., is treated with acetyl chloride of formula FF-1 to give the amide of formula FF-8.Treatment of the compound of formula FF-8 with $TiCl_4$ followed by treatment with a trialkyamine followed by the addition of commercially available trimethylacetaldehyde affords the compound of formula FF-9. Addition of the amide of formula FF-9 to a tetrahydrofuran solution containing commercially available $CuBr/(CH_3)_2S$ and 3-[bis(trimethylsilyl)amino] phenylmagnesium chloride at −20° C. affords a mixture of compounds of formulae FF-10a and FF-10b. Treatment of the aniline of formula FF-10b with benzyl bromide and sodium carbonate in a water/methylene chloride mixture at reflux; or, potassium carbonate in refluxing acetonitrile, affords the compound of formula FF-11 Treatment of the compound of formula FF-11 with $TiCl_4$ in methylene chloride followed by the addition of a tertiary amine base then addition of 2-methyl-2-methoxy-1,3-dioxolane affords an intermediate dioxolane (see W-8 in Chart W) which is treated with mild acid to give the compound of formula FF-12. Treatment of the compound of formula FF-12 with $TiCl_4$, then a tertiary amine base, followed by addition of either 4-heptanone or 1-phenyl-3-hexanone, affords the aldol product of formula FF-13. Treatment of the compound of formula FF-13 with either sodium hydride or potassium tert. butoxide in an ether solvent then affords the compound of formula FF-14. The compound of formula FF-14 is then hydrogenated under an atmosphere of hydrogen in the presence of a Pd on carbon catalyst to give the compound of formula FF-15. Finally, treatment of the compound of formula FF-15 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula FF-16, wherein R_1 is, e.g., propyl or phenethyl.

CHART GG

Intermediate of formula GG-6 and final products of formula GG-16 are prepared as described in Chart FF with the exception that the (R)-(−)-4-phenyl-2-oxazolidinone and the (R)-(+)-4-benzyl-2-oxazolidinone chiral auxiliaries are used.

CHART HH

The compound of formula HH-1 (W-6), prepared as described in Chart W, is converted to the ester of formula HH-2 wherein R is t-Bu by addition of potassium t-butoxide to a solution of the compound of formula HH-1 in tetrahydrofuran at 0° C. The compound of formula HH-2 wherein R is t-Bu may also be prepared from HH-1 in two steps. First, the oxazolidinone group is cleaved by treatment of the compound of formula HH-1 with lithium hydroxide and hydrogen peroxide at 0° C. in tetrahydrofuran and water. Next, the acid intermediate is treated with N,N-dimethylformamide t-butylacetal in refluxing benzene to produce the ester of formula HH-2 (R is t-Bu). The ester of formula HH-2 wherein R is Me is prepared by heating a mixture of titanium tetrachloride and HH-1 in methanol. The compound of formula HH-3 is prepared by treatment of the ester of formula HH-2 with lithium diisopropylamide or sodium hexamethyldisilylazide to form an enolate, which is then trapped by ethyl formate to give the compound of formula HH-3. Treatment of this intermediate with tosyl chloride in 1,2-dimethoxyethane gives the compound of formula HH-4, which is then converted to the sulfur derivative of formula HH-5 by treatment with a mixture of potassium hydride and thiophenol in tetrahydrofuran. The compound of formula HH-5 is then deprotonated using t-butyllithium in tetrahydrofuran at low temperature. Addition of the epoxide of formula HH-6 (BB-7), prepared as described in Chart BB, and an equivalent of boron trifluoride diethyl etherate affords the compound of formula HH-7. This intermediate is cyclized to the compound of formula HH-8 in situ, or it is isolated and treated with sodium hydride in tetrahydrofuran to produce the cyclic compound of the formula HH-8. The sulfur group is then hydrolyzed using either sodium hydroxide in acetonitrile or aqueous copper chloride to give the dihydropyrone derivative of formula HH-9. The benzyl protecting groups are then removed by catalytic hydrogenation using 10% palladium on carbon in ethyl acetate. The resulting amine of formula HH-10 is converted to the desired sulfonamide derivative of formula HH-11 by treatment with 5-cyanopyridine-2-sulfonyl chloride, prepared using the methods described in Chart O, and pyridine in dichloromethane.

CHARTS II–OO

The diastereomer of formula II-7 is prepared according to Chart II by procedures analogous to those described for the preparation of the diastereomeric product in Chart HH. Likewise, stereoisomers of formulae JJ-11, KK-7, LL-11, MM-7, NN-11, and OO-7 are prepared according to Charts JJ, KK, LL, MM, NN, and OO, respectively, by procedures analogous to those described in Chart HH.

CHART PP

The compound of formula PP-4 (HH-8) is also generated as described in Chart PP. The acid of formula PP-2 is prepared by treatment of the t-butyl ester of formula PP-1 (HH-5), prepared as described in Chart HH, with aqueous acid. The compound of formula PP-2 is then treated with t-butyllithium in tetrahydrofuran at low temperature to produce a dianionic intermediate, which is treated with the epoxide of formula PP-3 (BB-7), prepared as described in Chart BB, and an equivalent of boron trifluoride diethyl etherate to afford the compound of formula PP-4 (HH-8).

CHARTS QQ–WW

The diastereomer of formula QQ-3 (II-4) is prepared according to Chart QQ by procedures analogous to those

described for the preparation of the diastereomeric product in Chart PP. Likewise, stereoisomers of formulae RR-4 (JJ-8), SS-3 (KK-4), TT-4 (LL-8), UU-3 (MM-4), VV-4 (NN-8), and WW-3 (OO-4) are prepared according to Charts RR, SS, TT, UU, VV, and WW, respectively, by procedures analogous to those described in Chart PP.

CHART XX

The compound of formula XX-6 (HH-9) is also generated as described in Chart XX. The compound of formula XX-1 (HH-2), prepared as described in Chart HH, is heated neat in commercially-available tris(dimethylamino)methane, bis (dimethylamino)-methoxymethane or t-butoxy-bis (dimethylamino)methane to generate the intermediate of formula XX-2. One equivalent of t-butyllithium is added to a solution of this ester in tetrahydrofuran at low temperature to produce an anionic intermediate, which is treated with the epoxide of formula XX-3 (BB-7), prepared as described in Chart BB, and an equivalent of boron trifluoride diethyl etherate to afford the compound of formula XX-4. The intermediate of formula XX-4 is cyclized to the dihydropyrone intermediate XX-5 in situ, or XX-4 is isolated and cyclized by treatment with potassium t-butoxide or sodium hydride in tetrahydrofuran. Likewise, intermediate XX-5 is hydrolyzed in situ to form the compound of formula XX-6 (HH-9), or it is isolated and converted to the dihydropyrone of formula XX-6 (HH-9) by treatment with aqueous acid or aqueous base.

CHARTS YY–EEE

The diastereomer of formula YY-5 (II-5) is prepared according to Chart YY by procedures analogous to those described for the preparation of the diastereomeric product in Chart XX. Likewise, stereoisomers of formulae ZZ-6 (JJ-9), AAA-5 (KK-5), BBB-6 (LL-9), CCC-5 (MM-5), DDD-6 (NN-9), and EEE-5 (OO-5) are prepared according to Charts ZZ, AAA, BBB, CCC, DDD, and EEE, respectively, by procedures analogous to those described in Chart XX.

CHART FFF

The diastereomers of formulae FFF-5 and FFF-7 are also prepared by separation of a diastereomeric intermediate. The diastereomeric mixture of formula FFF-1 (W-11), prepared as described in Chart W, is separated into the single diastereomers of formulae FFF-2 (less polar diastereomer) and FFF-3 (more polar diastereomer) using a preparative chiral HPLC column. The benzyl protecting groups of compounds FFF-2 and FFF-3 are then removed by catalytic hydrogenation using 10% palladium on carbon in ethyl acetate to form the amines of formulae FFF-4 and FFF-6, respectively. The amine intermediates are then converted to the desired sulfonamide derivatives of formulae FFF-5 (HH-11) and FFF-7 (II-7), respectively, by treatment with 5-cyanopyridine-2-sulfonyl chloride, prepared using the methods described in Chart O, and pyridine in dichloromethane.

CHART GGG

The m-nitrocinnamic acid chloride (available from the treatment of the commercially available acid with oxylal chloride) of formula GGG-1 is added to an ether solution of the lithiooxazolidinone of formula GGG-2 (readily available from the treatment of commercially available (R)-(+)-4-benzyl-2-oxazolidinone with n-butyl lithium) to afford the compound of formula GGG-3. The compound of formula GGG-3 is treated with either $SnCl_2.2H_2O$ in ethanol or iron powder in a mixture of ethanol/water and containing ammonium chloride, to effect the reduction of the nitro group to the corresponding amine found in the compound of formula GGG-4. The compound of formula GGG-4 is treated with excess benzyl bromide in the presence of potassium or sodium carbonate in an organic solvent (with methylene chloride/water also being added) to yield the compound of formula GGG-5. Addition of a THF solution of the compound of formula GGG-5 to a THF/dimethylsulfide mixture containing the cuprate reagent prepared from ethyl magnesium bromide and copper bromide/dimethyl sulfide complex affords the compound of formula GGG-6. The compound of GGG-6 is then treated with $TiCl_4$, then a tertiary amine, followed by the addition of 2-methyl-2-methyoxy-1,3-dioxolane of formula GGG-7 to yield the compound of formula GGG-8. Treatment of the compound of formula GGG-8 with perchloric acid then yields the compound of formula GGG-9. Alternately, the compound of formula GGG-6 is treated with a strong base such lithium diisopropylamide in an ether solvent below room temperature and added to a solution of acetyl chloride (also in an ether solvent and cooled to below room temperature) to yield the compound of formula GGG-9. The compound of formula GGG-9 is treated with $TiCl_4$ in methylene chloride followed by the addition of a tertiary amine, then addition of either 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula GGG-10. The compound of formula GGG-10 is then treated with either sodium hydride or potassium tert-butoxide in an ether solvent to yield the compound of formula GGG-11. The compound of formula GGG-11 is then hydrogenated to yield the compound of formula GGG-12. The compound of formula GGG-12 is then converted to the final title compound by treatment with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provide the final compound of formula GGG-13, wherein R_1 is, e.g., n-propyl or phenethyl.

Alternatively, addition of the compound of formula GGG-5 to a THF/dimethylsulfide solution containing a mixture of tert-butyl magnesium chloride and copper bromide/dimethylsulife complex at below 0° C. yields a mixture of compounds of formulae GGG-14a and GGG-14b. Both the compounds of formula GGG-14a and GGG-14b are converted to the final products GGG-19 and GGG-20 using the methodology described in Chart GGG for the synthesis of the C-3 ethyl compound of formula GGG-13.

CHART HHH

The final compounds of formula HHH-13, HHH-19 and HHH-20 are prepared in the same manner as described for the final compounds in Chart GGG.

CHART III

The commercially available acid of formula III-1 is converted to the compound of formula III-2 by treatment with oxalyl chloride. The acid chloride of formula III-3 is then coupled to the lithio oxazolidinone of formula III-3 (readily available from the treatment of commercially available (S)-(−)-4-benzyl-2-oxazolidinone with n-butyl lithium in an ether solvent) to yield the compound of formula III-4. Addition of the amide of formula III-4 to a tetrahydrofuran solution containing commercially available copper bromide/dimethyl sulfide complex and 3-[bis(trimethylsilyl)amino]

phenylmagnesium chloride at −20° C. affords the compounds of formula III-5a and III-5b upon acid workup. These compounds are separable by silica gel chromatography. The compound of formula III-5a is treated with benzyl bromide in either acetonitrile or a methylene chloride/water mixture in the presence of either potassium or sodium carbonate to yield the compound of formula III-6. The compound of formula III-6 is treated with $TiCl_4$ in methylene chloride followed by the addition of a tertiary amine and then 2-methyl-2-methoxy-1,3-dioxolane of formula III-7 is added to yield the compound of formula III-8. Treatment of the compound of the formula III-8 with an acid such as perchloric acid then yields the compound of formula III-9. Treatment of the compound of formula III-9 with $TiCl_4$ in methylene chloride then addition of a tertiary amine, followed by the addition of either 4-heptanone or 1-phenyl-3-hexanone then affords the compound of formula III-10. Treatment of the compound of formula III-10 with either sodium hydride or potassium tert. butoxide then affords the compound of formula III-11. The compound of formula III-11 is hydrogenated to afford the compound of formula III-12. Finally, treatment of the compound of formula III-12 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula III-13, where in R_1 is, e.g., propyl or phenethyl.

In an analogous fashion, starting with the compound of formula III-5b, the final compound of formula III-14 is also prepared.

CHART JJJ

The final compounds of formula JJJ-13 and JJJ-14 are prepared using the methodology described in Chart III.

CHART KKK

The compound of formula KKK-1 (same as JJJ-9) is treated with $TiCl_4$ in methylene chloride followed by the addition of a tertiary amine. To that solution is added commercially available hydrocinnamaldehyde to afford the compound of formula KKK-2. The compound of formula KKK-2 is oxidized (e.g. $Me_2SO—SO_3$/pyridine) to yield the compound of formula KKK-3. The compound of formula KKK-3 is treated with propylmagnesium chloride (where R_1 is, e.g., phenyl) to yield the compounds of formula KKK-4a and KKK-4b. Depending on the specific reaction conditions, the ratio of KKK-4a/KKK-4b varies. Alternatively, addition of allylzinc bromide or allylsilane in the presence of $TiCl_4$ or n-Bu_4NF (see Taniguchi et. al. Chemistry Letters 2135, 1992) to the compound of formula KKK-3, followed by hydrogenation, also yields the compounds of formula KKK-4a and KKK-4b. Depending on the specific reaction conditions the ratio of KKK-4a and KKK-4b vary. The compound of KKK-4a is treated with either sodium hydride or potassium tert. butoxide to yield the compound of formula KKK-5. It is also possible that upon treatment of KKK-3 with allyl zinc bromide, allyl silane or propylmagnesium chloride the intermediate metal alkoxide (metals being magnesium, zinc and titanium) will undergo spontaneous cyclization to yield an unsaturated intermediate which upon hydrogenation leads directly to KKK-5 without the isolation of KKK-4a. The compound of formula KKK-5 is hydrogenated to yield the compound of formula KKK-6. Finally, treatment of the compound of formula KKK-6 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula KKK-7a, wherein, e.g., R_1 and R_2 are phenyl or propyl, respectively.

In an analogous manner to that described for the conversion of the compound of formula KKK-4a to the compound of formula KKK-7a, the compound of formula KKK-4b is converted to the final product of formula KKK-7b.

In an analogous manner to that described for the conversion of the compound of formula KKK-1 to final products of the formula KKK-7a and KKK-7b, the compounds of formula KKK-14a and KKK-14b, wherein R_1 and R_2 are, e.g., methyl or phenethyl, respectively, are prepared by starting with the compound of formula KKK-8 (same as III-6).

In an analogous manner to that described for the conversion of the compound of formula KKK-1 and the compound of formula KKK-8 (each containing the 4-benzyl-2-oxazolidinone auxillary) to the final products of the formulae KKK-7a and KKK-7b, and the final formulae KKK-14a and KKK-14b respectively, the compounds of the formula KKK-15 and the compound of the formula KKK-19 (each containing the 4-phenyl-2-oxazolidinone auxillary) are converted to the final products of the formula KKK-7a and K-7b, and the final products of formula KKK-14a and KKK-14b, respectively, wherein R_1 and R_2 are, e.g., methyl or phenethyl, respectively.

CHART LLL

The compound of formula LLL-1 (same as: wherein R is phenyl, AA-1; wherein R is benzyl, GGG-5) is added to a THF solution of commercially available copper bromide/dimethylsulfide complex and tert. butylmagnesium chloride below 0° C. to afford the compound of formula LLL-2 as the major diasteromeric product. Where R is defined as benzyl in the compound of formula LLL-2, that compound is treated with $TiCl_4$ in methylene chloride below 0° C. followed by the addition of a tertiary amine, then the addition of 2-methyl-2-methoxy-1,3-dioxolane to yield the compound of formula LLL-3. The compound of formula LLL-3 is treated with a protic acid to afford the compound of formula LLL-4. The compound of formula LLL-4 is treated with $TiCl_4$ in methylene chloride below 0° C. followed by the addition of an amine base, then addition of either 4-heptanone or 1-phenyl-3-hexanone affords the compound of formula LLL-5 wherein R_1 is, e.g., n-propyl or phenethyl, respectively. Treatment of the compound of formula LLL-5 with either sodium hydride or potassium tert. butoxide in an ether solvent affords the pyrone of formula LLL-6. Hydrogenation of the compound of formula LLL-6 using, e.g. a Pd on carbon as the catalyst, affords the compound of formula LLL-7. Finally, treatment of the compound of formula LLL-7 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula LLL-8, wherein R_1 is, e.g., propyl or phenethyl.

The compound of formula LLL-2, where R is phenyl, is treated with $TiCl_4$ in methanol to yield the compound of formula LLL9. The compound of formula LLL-9 is treated with a base to effect hydrolysis to give the compound of formula LLL-10. The acid of formula LLL-10 is treated with methyl lithium in an ether solvent to yield the compound of formula LLL-11. The ketone of formula LLL-11 is treated with $TiCl_4$ in methylene chloride below 0° C. followed by the addition of an amine base, then addition of either

4-heptanone or 1-phenyl-3-hexanone, to give the compound of formula LLL-12 wherein R_1 is, e.g., n-propyl or phenethyl, respectively. The compound of formula LLL12 is treated with $TiCl_4$ in methylene chloride below 0° C. followed by the addition of an amine base, then the addition of trimethyl orthoformate to yield the compound of formula LLL-13. The compound of formula LLL-13, in an organic solvent such as THF or methylene chloride, is treated with a base followed by the addition of trimethylsilyl chloride. The solvent is removed from the aforementioned reaction and the resulting protected tertiary alcohol is oxidized (e.g. Ru cat./t-BuOH (see Murahashi et. al. Chemistry Letters 2237, 1992); tritylperchlorate/methylene chloride (see Mukaiyama et. al. Chemistry Letters 1255, 1985), ozone/methylene chloride (see Can. J. Chem. 49, 2465, 1971)) to afford the lactone LLL-6 directly or in a two step sequence where the intermediate ester is lactonized with the aid of either sodium hydride, potassium tert. butoxide or n-Bu_4NF in an ether solvent. The conversion of the compound of formula LLL-6 to the final product is described above.

Following the same strategy the compound of formula LLL-16 is converted to the final products of formula LLL-23 wherein R_1 is propyl or phenethyl.

CHART MMM

The diastereomers of formulae MMM-5 and MMM-7 are also prepared by separation of a diastereomeric mixture of these two compounds. Alternatively, the diastereomeric mixture of formula MMM-1 (X-11 where R_1 is, e.g., phenethyl) prepared as described in Chart X, is separated into the single diastereomers of formulae MMM-2 and MMM-3 using a preparative chiral HPLC column. The benzyl protecting group groups of compounds MMM-2 (less polar diastereomer) and MMM-3 (more polar diastereomer) are then removed by catalytic hydrogenation using 10% palladium on carbon in ethyl acetate to form the amines of formulae MMM-4 and MMM-6, respectively. The amine intermediates are then converted to the desired sulfonamide derivatives of formulae MMM-5 and MMM-7, respectively, by treatment with 5-trifluoromethyl-2-pyridinylsulfonyl chloride, prepared using the methods described in Chart O, and pryidine in methylene chloride.

CHART NNN

The commercially available (1R,2S)-(−)ephedrine of formula NNN-2 is treated with triethylamine and the acid chloride of formula NNN-1 (W-2), prepared as described in Chart W, to afford the amide of formula NNN-3. A t-butyl methyl ether solution of this amide at 0° C. is treated sequentially with 1.1 equivalents of propyl magnesium chloride and 2.0 equivalents of 3-[bis(trimethylsilyl)amino] phenyl magnesium chloride, stirred for 3 hours at 0° C., washed with ammonium chloride solution and concentrated in vacuo. The residue is then stirred with silica gel in chloroform to afford the compound of formula NNN-4. Alternatively, the above reaction mixture may be washed with 1N hydrochloric acid solution during the workup instead of ammonium chloride solution to generate the compound of formula NNN-4. The amine is then converted to the derivative of formula NNN-5 by heating a mixture of the compound of formula NNN-4, 2.2 equivalents of benzyl bromide and 2.2 equivalents of sodium carbonate in acetonitrile. The intermediate of formula NNN-5 is then treated with 2 equivalents of lithium diisopropylamide in tetrahydrofuran to form the lithium enolate, which is trapped with acetyl chloride to afford the b-ketoamide of formula NNN-6. A solution of this amide in methylene chloride at low temperature may be treated with 1 equivalent of titanium tetrachloride and 1 equivalent of diisopropylethylamine, followed by 4-heptanone to generate the compound of formula NNN-7. Conversion of the amide of formula NNN-7 to the dihydropyrone of formula NNN-8 may be accomplished with either sodium hydride in tetrahydrofuran or with aqueous acid. The benzyl protecting groups may then be removed by catalytic hydrogenation using 10% palladium on carbon in ethyl acetate. The resulting amine of formula NNN-9 is converted to the desired sulfonamide derivative of formula NNN-10 (W-12) by treatment with 5-trifluoromethylpyridine-2-sulfonyl chloride, prepared using the methods described in Chart O, and pyridine in dichloromethane.

CHART OOO

The compound of formula OOO-7 (NNN-8) may also be generated as described in Chart OOO. The amide of formula OOO-1 (NNN-5) is treated with aqueous acid to afford the compound of formula OOO-2. The methyl ester of formula OOO-3 is formed from the compound of formula OOO-2 using catalytic acid in methanol. Treatment of the methyl ester of formula OOO-3 with lithium diisopropylamide, followed by trimethylsilyl chloride gives the compound of formula OOO-4. Treatment of this intermediate with either 2-methoxy-2-methyl-1,3-dioxolane followed by hydrolysis or treatment with acetyl chloride affords the β-keto ester of formula OOO-5. This β-keto ester is converted to the compound of formula OOO-6 by treatment of either the titanium enolate (formed using 1 equivalent of titanium tetrachloride and 1 equivalent of diisopropylethylamine in methylene chloride at low temperature) or the lithium dianion (formed using 2 equivalents of lithium diisopropylamide in tetrahydrofuran at low temperature) with 4-heptanone. The dihydropyrone of formula OOO-7 (NNN-8) is formed by treatment of the compound of formula OOO-6 with either sodium hydride in tetrahydrofuran or aqueous base.

CHART PPP

Reduction of the commercially available ethyl 4,4,4-trifluorobutyrate of formula PPP-1, with DiBAL-H followed by in situ alkylation with 2-phenethyl magnesium bromide or chloride produces the alcohol of formula PPP-2. Swern oxidation of the alcohol gives the ketone of formula PPP-3. The ketone is converted to the dihydropyrone of formula PPP-4 by alkylation with the dianion of methyl acetoacetate followed by saponification to the acid and lactonization with base.

CHART QQQ

The aluminum trichloride catalyzed reaction of the dihydropyrone of formula QQQ-1 (PPP-4), prepared as described in Chart PPP, with the CBZ-protected 3-aminobenzaldehyde (which is available from the reaction of benzyl chloroformate with commercially available 3-aminobenzaldehyde) of formula QQQ-2 and subsequent reaction with trialkyl aluminums or Grignard reagents in the presence of cuprous bromide-dimethylsulfide complexes provides compounds of formula QQQ-3. The individual stereoisomers are separated by HPLC using a chiral stationary phase to give the four possible stereoisomers of formula QQQ-4, QQQ-5, QQQ-6, and QQQ-7. Transfer hydrogenation of each stereoisomer with Pd/C and ammonium formate gives the amines of formula QQQ-8, QQQ-9, QQQ-10, and QQQ-11. Treatment of the amines with sulfonyl chlorides of

general formula QQQ-12 and pyridine in methylene chloride provides compounds of general formula QQQ-13, QQQ-14, QQQ-15, and QQQ-16, wherein R_2 is, e.g., 5-cyano-2-pyridinyl, 1-methyl-4-imidazolyl, or 5-amino-2-pyridinyl.

CHART RRR

The procedure for the preparation of compounds of formula RRR-11 to RRR-15 is described in Chart RRR. The pyrone RRR-A is coupled to the Cbz protected benzaldehyde RRR-B in THF with $AlCl_3$ followed by treatment of the resulting intermediate with R_1MgX where X=Br or Cl in THF with added $CuBr.Me_2S$ to give RRR-1. De-protection of the resulting intermediate with 10% Pd/C in methanol with added ammonium formate gives RRR-2. Separation of the racemic compound RRR-1 into its 4 enantiomers gives RRR-3 to RRR-6. De-protection of the resulting intermediates with 10% Pd/C in methanol with added ammonium formate gives the free amines RRR-7 to RRR-10. Treatment of the amines RRR-7 to RRR-10 and RRR-2 with an appropriate sulfonyl chloride gives the sulfonamides RRR-11 to RRR-14 and RRR-15, respectively.

CHART SSS

The procedure for the preparation of compounds of formula SSS-7 to SSS-9 is described in Chart SSS. The pyrone SSS-A is coupled to the Cbz protected benzaldehyde SSS-B in THF with $AlCl_3$ followed by treatment of the resulting intermediate with R_1MgX where X=Br or Cl in THF with added $CuBr.Me_2S$ to give SSS-1. De-protection of the resulting intermediate with 10% Pd/C in methanol with added ammonium formate gives SSS-2. Separation of the racemic compound SSS-1 into its 2 enantiomers gives SSS-3 to SSS-4. De-protection of the resulting intermediates with 10% Pd/C in methanol with added ammonium formate gives the free amines SSS-5 to SSS-6. Treatment of the amine with an appropriate sulfonyl chloride gives the sulfonamides SSS-7 to SSS-9.

CHART TTT

The procedure for the preparation of compounds of formula TTT-6 and TTT-7 is described in Chart TTT. The pyrone TTT-A is coupled to the Cbz protected benzaldehyde TTT-B in THF with $AlCl_3$ followed by treatment of the resulting intermediate with R_1MgX where X=Br or Cl in THF with added $CuBr.Me_2S$ to give TTT-1. Separation of the racemic compound TTT-1 into its 2 enantiomers gives TTT-2 and TTT-3. De-protection of the resulting intermediates with 10% Pd/C in methanol with added ammonium formate gives the free amines TTT-4 and TTT-5. Treatment of the amine with an appropriate sulfonyl chloride gives the sulfonamides TTT-6 and TTT-7.

CHART UUU

Reaction between commercially available thiourea in hot ethanol with commercially available 2-chloro-5-nitropyridine of formula UUU-1 affords the isothiourea compound of formula UUU-2. Treatment of the compound of formula UUU-2 with aqueous sodium carbonate and sodium hydroxide provides the thiol compound of formula UUU-3. Oxidation of the compound of formula UUU-3 with chlorine gas provides the sulfonyl chloride compound of formula UUU-4. Treatment of the compound of formula D-5 (e.g., the compound of formula T-4 wherein R_1 is 2-phenylethyl, R_2 is propyl, R_3 is tert-butyl) in dichloromethane with two equivalents of pyridine followed by one equivalent of the compound of formula UUU-4 gives the sulfonamide compound of formula UUU-5 (wherein R_1 is 2-phenylethyl, R_2 is propyl, R_3 is tert-butyl). Reduction of the compound of formula UUU-5 with palladium on carbon and ammonium formate affords the compound of formula UUU-6, which is the compound: 5-amino-N-[3-(1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide (Formula UUU-6: R_1 is 2-phenylethyl, R_2 is propyl, R_3 is tert-butyl).

CHART VVV

The compound of Formula VVV-1, which is 2-mercapto-5-carbamoylpyridine, is prepared via published procedure (J. Chem. Soc. 1948, 1939–1945). Treatment of a suspension of this compound in dilute hydrochloric acid with chlorine gas at 0° provides the sulfonyl chloride of Formula VVV-2.

CHART WWW

Amines of the generic formula WWW-1 are reacted with benzyl chloroformate to provide CBZ derivatives WWW-2. The individual stereoisomers of formula WWW-2 are generally separated by chiral HPLC methods, and then converted back to the free amines WWW-3 via hydrogenolysis. Sulfonation of the amines in the usual manner known to one of ordinary skill in the art provides the final compounds of formula WWW-4, in stereochemically pure form.

CHART XXX

Dihydropyrone XXX-1, which is prepared by procedures analogous to those in described in Preparations 17 and 84, is condensed with meta-nitrobenzaldehyde in the presence of aluminum trichloride to provide the benzylidene intermediate XXX-2. Conjugate reduction of the double bond using sodium cyanoborohydride, followed by reduction of the nitro group via catalytic hydrogenation, affords amine of formula XXX-4, which is converted to the sulfonamides XXX-5 by treatment with the appropriate sulfonyl chloride in dichloromethane and pyridine.

CHART YYY

Dihydropyrones of Formula YYY-1, wherein R_1 and R_2 are propyl or phenethyl, and which are synthesized as described in Preparation 84, are condensed with the aldehyde of Formula B-2 using aluminum trichloride to provide the benzylidene intermediates of formula YYY-2. Conjugate addition of tert-butylmagnesium chloride in the presence of copper (I) bromide-dimethyl sulfide provides compounds of Formula YYY-3. Hydrogenolytic deprotection affords amines of formula YYY-4, which are converted to the sulfonamides of formula YYY-5 using the appropriate sulfonyl chloride in dichloromethane with added pyridine. The procedures used are analogous to those described for Chart D.

CHART ZZZ

Polymeric meta-aminobenzaldehyde is protected by treating with benzyl bromide and potassium carbonate in acetonitrile at reflux to yield the compound of formula ZZZ-2. A vinyl anion is generated from 2-bromovinyltrimethylsilane of formula ZZZ-3 by treatment with t-butyl lithium at −78° C. to −20° C. The vinyl anion so generated is cooled to −78° C. and the diprotected meta-aminobenzaldehyde of formula ZZZ-2 is added to afford the desired allylic alcohol of

formula ZZZ-3. The alcohol is easily converted to the acetate or carbonate of formula ZZZ-5 by standard means (e.g., CH_3COCl, pyridine, CH_2Cl_2, 0° C.). These substrates participate in palladium catalyzed allylic substitutions as delineated in Charts AAAA–CCCC (C. G. Frost; J. Howarth; J. M. J. Williams, Tetrahedron: Asymmetry (1992) 3:1089–1122).

CHART AAAA

The sodium salt of methyl acetoacetate of formula AAAA-1 generated by treating methyl acetoacetate with sodium hydride at 0° C. in either DMF or THF acts as the nucleophile in a palladium catalyzed allylic substitution. If this reaction is run in the presence of palladium allyl chloride dimer of formula AAAA-3 as the palladium source and a chiral phosphine ligand (P. von Matt; A. Pfaltz, Angew. Chem. Int. Ed. Engl. (1993) 32:566–568), a kinetic resolution of the starting allylic acetate or carbonate results in the synthesis of optically enriched allylated product of formula AAAA-4. If the reaction with nucleophile is slow, the acetate generated from formation of the pi-allyl palladium intermediate isomerizes the two possible diastereomeric pi-allyl complexes so that a stereoselective synthesis of the allylated product occurs (B. M. Trost; P. E. J. Strege, Am. Chem. Soc. (1977) 99:1649). Treatment of the resulting vinyl silane of formula AAAA-4 with para-toluenesulfonic acid in acetonitrile at reflux affords the desilylated olefin of formula AAAA-5. The dihydropyrone product of formula AAAA-7 is formed by generating the dianion of the β-ketoester under standard conditions (J. R. Peterson; T. J. Winger; C. P. Miller, Syn. Comm. (1988) 18(9):949–963), (NaH, n-butyllithium, THF) and quenching with an appropriate symmetrical ketone of formula AAAA-6 (such as 4-heptanone). Hydrolysis of the ester (0.1N NaOH/THF) and acidic work-up provide the dihydropyrone product of formula AAAA-7. Standard hydrogenation conditions reduce the olefin and deprotect the amine. Subsequent treatment of the amino compound with the appropriate sulfonyl chloride of formula AAAA-8 (pyridine, CH_2Cl_2) provides the desired sulfonamide protease inhibitor of formula AAAA-9.

CHART BBBB

Alternatively, the palladium catalyzed allylic substitution may be performed with the sodium anion of the requisite dihydropyrone J. R. (Peterson; T. J. Winger; C. P. Miller, Syn. Comm. (1988) 18(9):949–963) of formula BBBB-1 (dihydropyrone, NaH, THF or DMF, 0° C.) as the nucleophilic partner. Once again, if palladium allyl chloride dimer of formula BBBB-3 and a chiral phosphine ligand (P. von Matt; A. Pfaltz, Angew. Chem. Int. Ed. Engl. (1993) 32:566–568) are employed as catalyst, a kinetic resolution results in the synthesis of optically pure allylated dihydropyrone of formula BBBB-4; and a stereoselective synthesis of the allylated product will occur if the reaction with nucleophile is slow relative to isomerization of the two possible diastereomeric pi-allyl complexes by acetate generated from formation of the pi-allyl palladium intermediate. Subsequent, desilylation (p-TsOH, CH_3CN), olefin reduction and amine deprotection (H_2/Pd/C), and sulfonylation of the amine ($ArSO_2Cl$, pyridine, CH_2Cl_2) with a compound of the formula BBBB-5 provides the desired dihydropyrone protease inhibitor of formula BBBB-6.

CHART CCCC

Treatment of m-bis(benzyl)aminobenzoic acid of formula CCCC-1 with oxalyl chloride to form the acid chloride and reaction with bis(trimethylsilyl)acetylene and $AlCl_3$ in methylene chloride affords the propargylic ketone of formula CCCC-2. Asymetric reduction of the ketone with a chiral borane (H. C. Brown; Beeraraghavan Ramachandran, P. Acc. Chem. Res. (1992) 25:16–24) such as DIP chloride [(+) or (−)-β-chlorodiisopinocampheylborane] and acetylene reduction with REDAL provides the allylic alcohol of formula CCCC-3, primarily as a single enantiomer. Formation of the carbonate of formula CCCC-4 (methyl chloroformate, pyridine, CH_2Cl_2, 0° C.) and subjection to palladium catalyzed allylic substitution with the desired dihydropyrone of formula CCCC-5 as nucleophile affords primarily one enantiomer of the allylated dihydropyrone of formula CCCC-6 (retention of configuration) (T. Hayashi; T. Hagihara; M. Konishi; M. J. Kumada, Am. Chem. Soc. (1983) 105:7768–7770). This product is transformed into the desired protease inhibitor of formula CCCC-7 as previously described in Chart BBBB.

CHART DDDD

The known cycloalkylpyranones of formula DDDD-1 are prepared by acylation of the trimethylsilyl enol ether of the corresponding cycloalkyl ketone with malonyl dichloride as described in R. Effenberger, T. Ziegler, K.-H. Schonwalder, T. Kesmarszky, B. Bauer Chem. Ber. 119:3394–3404 (1986). Catalytic hydrogenation of the cycloalkylpyranones of formula DDDD-1 with platinum oxide (PtO_2) in acetic acid produces the cycloalkyldihydropyrones of Formula DDDD-2. The intermediate of formula DDDD-3 is then formed by aluminum chloride ($AlCl_3$) catalyzed condensation of the compound of formula DDDD-2 with 3-nitrobenzaldehyde, which is commercially available. Subsequent reaction of the intermediate of formula DDDD-3 with trialkyl aluminums in the presence of copper bromide-dimethyl sulfide complex (CuBr—Me_2S) or zinc reagents generated from zinc metal, alkyl halide, cuprous cyanide (CuCN) and lithium chloride (LiCl) provides compounds of formula DDDD-4 which contain a C-3a branched substituent. Catalytic hydrogenation of compounds of the formula DDDD-4 with Pd/C in ethanol (EtOH) provides the amine derivatives of the formula DDDD-5. Treatment of the compounds of formula DDDD-5 with sulfonyl chlorides of formula DDDD-6 and pyridine in methylene chloride (CH_2Cl_2) provides compounds of the formula DDDD-7 (e.g., wherein n is 1, 2, or 3; R_1 is ethyl or t-butyl; R_2 is 4-cyanophenyl or 5-cyano-2-pyridyl).

Procedures by which the compounds of the present invention are prepared are also described in International application, PCT/US93/10645, filed 9 Nov. 1993 (WO 94/11361, published 26 May 1994), and International application, PCT/US94/00938, filed 3 Feb. 1994 (WO 94/18188, published 18 Aug. 1994), both of which are incorporated by reference herein.

As is apparent to those of ordinary skill in the art, the compounds of the present invention can occur in several diastereomeric forms, depending on the configuration around the asymmetric carbon atoms. All such diastereomeric forms are included within the scope of the present invention.

Also, the dihydropyrones of the present invention can be separated into individual stereoisomers or prepared as individual diastereomers. A diastereomeric pair can be prepared wherein C-3α is a homogeneous center and C-6 is a mixture. All such enantiomeric and diastereomeric forms, and mixtures thereof, are included within the scope of the present invention.

The compounds of the present invention of formula I can exist in several tautomeric forms, including the particular enol forms as depicted by formula I and IA and the keto form of formula IB. (For formulas I, IA and IB, the dashed line indicates that a double bond may be present or absent.) All such tautomeric forms are included within the scope of the present invention. For compounds of the present invention which are 4-hydroxy-pyran-2-ones of formula VII, the enol form predominates. For compounds of the present invention which are 5,6-dihydro-4-hydroxy-pyran-2-ones of formula VI, a mixture of the enol and keto forms is commonly expected.

Also, the compounds of the present invention of formula II can exist in several tautomeric forms of the 4-hydroxy-pyrone ring, including the particular enol forms depicted by formulas II and IIA, and the particular keto form depicted by formula IIB, and mixtures thereof. All such tautomeric forms are included within the scope of the present invention.

The compounds of the present invention may be in either free form or in protected form at one or more of the remaining (not previously protected) carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the art. Examples of nitrogen and oxygen protecting groups are set forth in T. W. Greene, Protecting Groups in Organic Synthesis, Wiley, New York, (1981); J. F. W. McOmie, ed. Protective Groups in Organic Chemistry, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, Organic Synthesis, Verlag Chemie (1983). Included among the nitrogen protective groups are t-butoxycarbonyl (BOC), benzyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl and the like.

The present invention provides for compounds of formula I and II or pharmacologically acceptable salts and/or hydrates thereof. Pharmacologically acceptable salts refers to those salts which would be readily apparent to a manufacturing pharmaceutical chemist to be equivalent to the parent compound in properties such as formulation, stability, patient acceptance and bioavailability. Examples of salts of the compounds of formula I include acidic salts, such as sodium, potassium, lysine, arginine and calcium salts, and basic salts, such as the hydrochloride salt, wherein the R substituents in formula I contain a basic moiety. Examples of salts of the compounds of formula II include the hydrohalide salts, such as the hydrochloride and hydroiodide salts; and the sodium, potassium, calcium, lysine and arginine salts.

Also included as salts of the compounds of formulae I and II of the present invention are the bis-salts, such as the bis-arginine, bis-lysine, bis-sodium, bis-potassium and bis-calcium salts, provided that the compound contains, for example, —$NHSO_2$—, —SO_3H, —CONH—, —OH or COOH. The bis-sodium salt is most preferred.

The compounds of the present invention are useful for treating patients infected with human immunodeficiency virus (HIV) which results in acquired immunodeficiency syndrome (AIDS) and related diseases. For this indication, these compounds may be administered by oral, intranasal, transdermal, subcutaneous and parenteral (including intramuscular and intravenous) routes in doses of 0.1 mg to 100 mg/kg of body weight per day.

Those skilled in the art would know how to formulate the compounds of this invention into appropriate pharmaceutical dosage forms. Examples of the dosage forms include oral formulations, such as tablets or capsules, or parenteral formulations, such as sterile solutions.

When the compounds in this invention are administered orally, an effective amount is from about 0.1 mg to 100 mg per kg of body weight per day. Either solid or fluid dosage forms can be prepared for oral administration. Solid compositions, such as compressed tablets, are prepared by mixing the compounds of this invention with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methyl cellulose, or functionally similar pharmaceutical diluents and carriers. Capsules are prepared by mixing the compounds of this invention with an inert pharmaceutical diluent and placing the mixture into an appropriately sized hard gelatin capsule. Soft gelatin capsules are prepared by machine encapsulation of a slurry or solution of the compounds of this invention with an acceptable inert oil such as vegetable oil or light liquid petrolatum.

Pharmaceutically acceptable formulations of the disodium salts of the compounds of the present invention include: soft elastic capsules (SEC) containing a suspension of the salt; salt tablets; salt spray coated sucrose beads; or salt spray dried matrix with an enteric or non-enteric polymer.

Formulations of the compounds of the present invention, which present the compounds in free acid form, preferably contain the free acid in non-crystalline form. Examples of such formulations include: soft elastic capsules containing free acid solution; non-crystalline spray dried matrix of the free acid with an enteric or non-enteric polymer; or a solid non-crystalline matrix of free acid in polyethyleneglycol (PEG) or Gelucire 44/14 (Gattefosse, Saint Priest, France).

Syrups are prepared by dissolving the compounds of this invention in an aqueous vehicle and adding sugar, aromatic flavoring agents and preservatives. Elixirs are prepared using a hydroalcoholic vehicle such as ethanol, suitable sweeteners such as sugar or saccharin and an aromatic flavoring agent. Suspensions are prepared with an aqueous vehicle and a suspending agent such as acacia, tragacanth, or methyl cellulose.

When the compounds of this invention are administered parenterally, they can be given by injection or by intravenous infusion. An effective amount is from about 0.1 mg to 100 mg per kg of body weight per day. Parenteral solutions are prepared by dissolving the compounds of this invention in liquid vehicle and filter sterilizing the solution before placing in a suitable sealable vial or ampule. Parenteral suspensions are prepared in substantially the same way except a sterile suspension vehicle is used and the compounds of this invention are sterilized with ethylene oxide or suitable gas before it is suspended in the vehicle.

The exact route of administration, dose, or frequency of administration would be readily determined by those skilled in the art and is dependant on the age, weight, general physical condition, or other clinical symptoms specific to the patient to be treated.

Patients to be treated would be those individuals: 1) infected with one or more than one strain of a human immunodeficiency virus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) having either an asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isoporiasis, iii) bronchial and pulmonary-candidiasis including pneumocystis pneumonia, iv) non-Hodgkin's lymphoma, or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm^3 in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the compounds of this invention in the patient at all times and would continue until the occurrence of a second

symptomatic AIDS defining infection indicates alternate therapy is needed.

The utility of representative compounds of the present invention has been demonstrated in the biological tests described below:

The HIV protease screening assay is based on fluorescently labeled substrate which can be resolved from nonlabeled cleavage product using special beads coated with streptavidin. The substrate is biotinylated at the amino terminal arginine and fluorescently labeled with fluorescein isothiocynate (FITC) at the carboxyl terminal lysine. This assay has been employed to detect novel, nonpeptidic inhibitors of HIV-1 protease. Substrate (20 μl of 0.2 μM), sample (10 μl of desired concentration), and enzyme (10 μl of 0.1 μM) are added to a 96 well pandex plate. The assay is run in 0.1M sodium acetate buffer at pH 5.5 in the presence of 1.0M sodium chloride and 0.05% NP-40 with incubated in the dark for one hour at room temperature. Streptavidin coated polystyrene beads {40 μl of 0.1% (w/v)} are added and the plate is incubated in the dark for an additional half hour. The labeled cleavage product is separated from the unreacted substrate via filtration and is read on the Idexx screen machine. The data are analyzed by appropriate computer algorithms to ascertain percent inhibition values.

Determination of K_i values utilizes the same materials and equipment employed for percent inhibition studies. Twofold serial dilutions are made for a given inhibitor from 2, 3 or 4 starting concentrations with a total of 24, 36 or 48 individual inhibitor concentrations. These dilutions are performed utilizing the BioMek robotics system. The assay consists of 10 μL of 40 nM HIV-1 protease, 10 μL of the various inhibitor concentrations, and 20 μL of 200 μM substrate (40 uL total). The reaction is allowed to proceed for 90 min at room temperature, terminated with 40 μL of avidin beads and processed (supra vide). An inhibitor with a known K_i is run in parallel to verify the validity of the assay. The data is processed utilizing a computer program employing a nonlinear least square analysis of the data to generate the K_i values.

The % inhibition values and/or K_i values of representative compounds of the present invention tested in the HIV protease screening assay are listed in Table I below.

In the enzyme inhibition assay described above, the sensitivity of K_i value determination is in part limited by the ability to continue to lower the enzyme concentration for compounds with high binding affinity. To prevent de-dimerization at low enzyme concentration, a tandemly linked enzyme is prepared in which the two monomers are covalently linked by an appropriate stretch of amino acid residues. Using the latter enzyme, the sensitivity of the inhibition assay is improved since much lower enzyme concentration can be utilized, as compared to the condition using the wild-type enzyme.

Protocol for K_i value determination with tandem HIV protease: Due to the greater stability (no dedimerization) of the single chain tethered (tandem) HIV protease enzyme, in which the two monomeric units are engineered to be linked by a polypeptide stretch, the method for the determination of K_i values for inhibitors uses very low concentrations of enzyme (0.2 nM) and increased incubation times (96 hours) at room temperature to improve the sensitivity in the measurement of K_i values for very potent inhibitors. The starting inhibitor concentrations are determined based on preliminary enzyme inhibition screening results which estimate the expected potency of the inhibitor. Inhibitor concentrations are then prepared using the Biomek 1000 (Beckman) and the Quadra 96 (Tomtec). Substrate (biotinylated at the amino terminal arginine and fluorescently labeled with fluorescein at the carboxyl terminal lysine), inhibitor and the tandem enzyme are allowed to react in solution at pH 5.5 (buffers identical to those used with the native dimeric enzyme) in the dark for 96 hours. Streptavidin coated polystyrene beads are added to stop the reaction. The labeled cleavage product is separated from unreacted substrate via filtration. Residual fluorescence is quantitated with the Idexx SM2000 (Idexx) and the resulting data are analyzed using the NLLSF program.

The % inhibition values and/or K_i values of representative compounds of the present invention tested in the HIV protease screening assay and/or tandem HIV protease assay are listed in Table II below.

Several compounds of the present invention, such as N-[3-(1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide were tested in known human cell lines, such as human T-cell lines, e.g., MT4 and H9, which were infected with HIV-1_{IIIB}, and certain of these compounds were further tested in peripheral blood mononuclear cells (PBMC), which were infected with HIV-1_{JRCSF} (a clinical isolate). The compounds were found to inhibit retroviral replication.

The following compounds of the present invention are preferred:

5-Cyano-N-[3-(1-[5,6-dihydro-4-hydoxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-(1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-[1-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran- 3-yl)-2,2-dimethylpropyl)phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl) propyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl) phenyl]-5-cyano-2-pyridinesulfonamide

N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide

N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl) phenyl]-1-methyl-1H-imidazole-4-sulfonamide

5-cyano-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(R or S)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-amino-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-[6-(R or S)-propyl]-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide, or (3R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-phenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide, or (3R or S, 6R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Amino-N-[3-(1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3-(1-[6,6-diisobutyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

N-[3(R or S)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(R or S)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-Cyano-N-[3-(1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]cyclopropylmethyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(R or S)-(1-[6(R or S)-(2-[4-fluorophenyl]ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

N-[3(R or S)-(1-[5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-Amino-N-[3(R or S)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl) phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(R or S)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl) phenyl]-2-pyridinesulfonamide,

N-[3(R or S)-(1-[6,6-Bis(2-phenylethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3(R or S)-(1-[6,6-Bis(2-phenylethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide,

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-aminopyridine-2-sulfonamide

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide

The following compounds of the present invention are more preferred:

5-Cyano-N-[3-(1-[5,6-dihydro-4-hydoxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide

5-cyano-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide, or (3R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide, or (3R or S, 6R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Cyano-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

N-[3(R or S)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(R or S)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide, and

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide.

The following compounds of the present invention are most preferred (see Chart EEE):

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide of formula EEE-1,

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide of formula EEE-2,

N-[3(R or S)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(R or S)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide of formula EEE-3,

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide of formula EEE-4, or (3R or S, 6R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide of formula EEE-5, or (3R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide.

Also the following compounds of the present invention, which are readily prepared by the synthetic procedures set out herein, are most preferred:

(3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

(3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the Preparations and Examples below and throughout this document:

°C. is degrees Centigrade.
^{1}H-NMR is proton nuclear magnetic resonance spectrum.
^{13}C-NMR is carbon nuclear magnetic resonance spectrum.
δ is chemical shift (parts per million) relative to TMS.
$AlCl_3$ is aluminum chloride.
Anal. is analytical data.
Br is benzyl.
CBZ is benzyloxycarbonyl.
$CDCl_3$ is deuterio-chloroform.
CD_3OD is deuterio-methanol.
CH_2Cl_2 is methylene chloride.
cm^{-1} is reciprocal centimeters.
$CuBr_2$ is cupric bromide.
DMSO is dimethylsulfoxide.
$DMSO_{D6}$ is deuterio dimethylsulfoxide.
EI MS is electron impact mass spectroscopy.
EtOAc is ethyl acetate.
Et_3Al is triethyl aluminum.
FAB MS is fast-atom-bombardment mass spectroscopy.
HCl is hydrochloric acid.
H_2O is water.
HOBT is 1-hydroxybenzotriazole hydrate.
HRMS is high-resolution mass spectroscopy.
KOH is potassium hydroxide.
M is molar (concentration).
MeOH is methanol.
Me_2S is dimethyl sulfide.
mg is milligram.
$MgSO_4$ is magnesium sulfate.
mL is milliliter.
mmHg is millimeter of mercury.
MP is melting point.
N is normal (concentration).
NaCl is sodium chloride.
NaOH is sodium hydroxide.
NaH is sodium hydride.
$NaHCO_3$ is sodium bicarbonate.
Na_2CO_3 is sodium carbonate.
Na_2SO_4 is sodium sulfate.
NH_4Cl is ammonium chloride.
Pd/C is palladium on charcoal.
R_f is chromatographic movement relative to solvent front.
TFA is trifluoroacetic acid.
THF is tetrahydrofuran.
TMS is tetramethyl silane.

The following Preparations and Examples illustrate the present invention:

PREPARATION 1

Cyclopropyl-(3-nitrophenyl)methanone (Formula A-2) Refer to Chart A

A 500-mL, three-necked, round-bottomed flask with a gas outlet and a 250-mL pressure-equalizing addition funnel is charged with cyclopropyl phenyl ketone of formula A-1 (30 mL) and cooled to −40° C. The addition funnel is charged with nitric acid (180 mL), which is added to the reaction mixture dropwise over 2 h. The reaction mixture is stirred another 3.5 h at −40°–0° C., and then quenched by pouring onto 500 mL of ice. The mixture is extracted with three 150-mL portions of ethyl acetate. The organic layers are combined, washed with two 250-mL portions of saturated sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated to give 41.117 g of yellow solid in an orange oil. Recrystallization from 65 mL of methanol yields 20.664 g of the title product as light yellow crystals.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ8.85, 8.43, 8.33, 7.70, 2.72, 1.36–1.31, 1.20–1.14 ppm.

PREPARATION 2

Cyclopropyl-(3-aminophenyl)methanone (Formula A-3) Refer to Chart A

A 500-mL Parr hydrogenation flask is charged with 2.1 g of 10% platinum on carbon and a solution of the title product of Preparation 1 (20.6 g) in 250 mL of methanol. The reaction mixture is shaken for 50 min under 44 psi of hydrogen, then filtered through Celite twice. The light green solution is then concentrated to give 15.744 g of the title product as a green oil.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.42, 7.30–7.23, 6.88, 3.83, 2.63, 1.24–1.19, 1.05–0.99 ppm.

PREPARATION 3

N-[3-cyclopropylmethanone]benzenesulfonamide (Formula A-4) Refer to Chart A

A 500-mL, three-necked, round-bottomed flask with a nitrogen inlet is charged with the title product of Preparation 2 (15.7 g) and 200 mL of methylene chloride. Benzenesulfonyl chloride (12 mL) and pyridine (7.8 mL) are added, and the reaction mixture is stirred at room temperature for 45 min. 10% HCl (200 mL) is added to quench the reaction. The organic layer is separated, dried over magnesium sulfate, filtered, and concentrated to give 28.638 g of orange solid. Recrystallization from 75 mL of hot methylene chloride yields the title product (22.264 g) as a pink solid.

Physical characteristics are as follows:

MP 98°–101° C.

^{1}H NMR ($CDCl_3$) δ7.81–7.73, 7.62, 7.55–7.35, 2.60, 1.30–1.25, 1.10–1.03 ppm,

^{13}C NMR ($CDCl_3$) δ200.4, 138.8, 137.2, 133.0, 129.5, 129.0, 127.0, 125.1, 124.7, 120.5, 17.3, 12.1 ppm.

IR (mineral oil) 3239, 3222, 1653, 1449, 1339, 1259, 1176, 1165, 1093, 939, 687 cm^{-1}.

Elemental analysis, found: C, 63.70; H, 5.01; N, 4.78.

MS (EI) m/e 301, 260, 160, 141, 77.

For high resolution, found: 301.0772.

PREPARATION 4

N-[3-cyclopropylmethanol]benzenesulfonamide (Formula A-5) Refer to Chart A

A 500-mL, three-necked, round-bottomed flask with a nitrogen inlet is charged with the title compound of Preparation 3 (21.133 g), 200 mL of tetrahydrofuran, and 100 mL of ethanol. The flask is cooled to 0° C. in an ice bath, and sodium borohydride (10.6 g) is added in small portions over 20 minutes. The reaction mixture is stirred at room temperature for ca. 18 h, and then cooled again in an ice bath to 0° C. 10% HCl (100 mL) is added dropwise over 45 min, and the mixture is stirred another 1 h at 0° C. The reaction mixture is then extracted with three 100-mL portions of methylene chloride. The organic layers are combined, dried over magnesium sulfate, filtered and concentrated to give 25.015 g of pale yellow oil. Column chromatography on 150 g of silica gel (elution with 50–65% ether in hexane followed by 2–5% methanol in methylene chloride) yields 18.692 g of the title product as a white solid.

Physical characteristics are as follows:

MP 112°–114° C.

^{1}H NMR ($CDCl_3$) δ7.69, 7.42, 7.32, 7.25, 7.12, 7.05–6.96, 3.82, 3.19, 1.03–0.94, 0.51–0.46, 0.39–0.29, 0.19–0.16 ppm.

^{13}C NMR (DMSO) δ147.0, 139.7, 137.4, 132.9, 129.3, 128.6, 126.8, 121.8, 118.5, 117.8, 75.0, 19.2, 3.1, 2.3 ppm.

IR (mineral oil) 3523, 3249, 1449, 732 cm^{-1}.

Elemental analysis, found: C, 63.41; H, 5.79; N, 4.86.

MS (EI) m/e 303, 275, 262, 77.

For high resolution, found: 303.0935.

PREPARATION 5

4-Hydroxy-10-propyl-2H-cycloocta[b]pyran-2-one (Formula A-7) Refer to Chart A

A 250-mL, three-necked, round-bottomed flask with a nitrogen inlet and a 125-mL pressure-equalizing addition funnel is charged with diisopropyl amine (3.6 mL) and 15 mL of tetrahydrofuran. The addition funnel is charged with 4-hydroxy-2H-cycloocta[b]pyran-2-one of formula A-6 (2.292 g) and 35 mL of tetrahydrofuran. The flask is cooled to 0° C. in an ice bath, n-butyllithium (16.3 mL of 1.6M solution in hexanes) is added dropwise over 3 min, and the reaction mixture is stirred another 15 min at 0° C. The solution of 4-hydroxy-2H-cycloocta[b]pyran-2-one in THF is added dropwise over 35 min, and the reaction mixture is stirred for another 25 min at 0° C. Hexamethylphosphoramide (4 mL) is added in one portion, and iodopropane (1.3 mL) is added dropwise over 2 min. The reaction mixture is allowed to warm to room temperature and stirred for ca. 18 h. 30 mL of 10% HCl is added and the aqueous layer is separated. The pH of the aqueous layer is lowered from 10 to 2 with concentrated HCl, and the aqueous layer is extracted with two 50-mL portions of methylene chloride. The organic layers are combined, dried over magnesium sulfate, filtered, and concentrated to give an orange oil, which is partitioned between 100 mL of 1N sodium hydroxide and 50 mL of ether. The aqueous layer pH is adjusted from 14 to 1 with concentrated hydrochloric acid, and is then extracted with two 50-mL portions of methylene chloride. The organic layers are then combined, dried over magnesium sulfate, and concentrated to give an orange oil, which is diluted with 100 mL of ether and washed with three 25-mL portions of 10% HCl. The organic layer is then dried over magnesium sulfate, filtered, and concentrated to give 1.829 g of orange solid. Column chromatography on 100 g of silica gel (elution with 0–10% methanol in methylene chloride) gives 1.358 g of a pale orange solid. An additional column chromatography on 150 g of silica gel (elution with 10% ether and 1% acetic acid in methylene chloride) gives 0.705 g of the title product as a yellow solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ11.38, 5.68, 3.02–2.93, 2.20, 1.98–1.82, 1.73–1.58, 1.46–1.25, 1.24–1.08, 0.89 ppm.

^{13}C NMR ($CDCl_3$) δ172.3, 168.3, 165.3, 114.8, 89.7, 38.6, 36.0, 33.3, 30.1, 27.2, 25.5, 22.9, 21.0, 13.9 ppm.

IR (mineral oil) 1679, 1641, 1617, 1492 cm^{-1}.

Elemental analysis, found: C, 70.90; H, 8.36.

MS (EI) m/e 236, 208, 166.

For high resolution, found: 236.1414.

EXAMPLE 1

N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-10-propyl-2H-cycloocta[b]pyran-3-yl)methyl]phenyl] benzenesulfonamide (Formula A-8) Refer to Chart A

A 100-mL, three-necked, round-bottomed flask with a 35-mL pressure-equalizing addition funnel filled with 3 A molecular sieves and fitted with a reflux condenser and a nitrogen inlet is charged with the title compound of Preparation 5 (0.196 g), p-toluenesulfonic acid (0.040 g), and 30 mL of methylene chloride. The title product of Preparation 4 (0.252 g) is added, and the reaction mixture is heated to reflux for 2 h, then stirred at room temperature for an additional hour. The reaction mixture is then diluted with 20 mL of methylene chloride and washed with 60 mL of 1:1 saturated sodium bicarbonate and brine, 30 mL of water, and 30 mL of brine. The aqueous layers are combined and extracted with 30 mL of methylene chloride. The organic layers are then combined, dried over magnesium sulfate, filtered, and concentrated to give 0.576 g of crude material. Column chromatography on 35 g of silica gel (elution with 20–80% ether in hexane) yields 0.096 g of the title compound as a white solid.

Physical characteristics are as follows:

MP 87°–90° C. (decomposition).

MS (EI) m/e 521, 493, 380, 275, 262, 249, 144, 77.

For high resolution, found: 521.2236.

EXAMPLES 2–7

Following procedures analogous to those described above, the following additional compounds of the present invention are prepared:

2) 4-Cyano-N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-(R or S)-10-propyl-2H-cycloocta[b]pyran-3-yl)methyl]phenyl] benzenesulfonamide

3) 4-Cyano-N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-(R or S)-10-cyclopropylmethyl-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl] benzenesulfonamide

4) 4-Cyano-N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-(R or S)-10-benzyl-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl] benzenesulfonamide

5) N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-(R or S)-10-propyl-2H-cycloocta[b] pyran-3-yl)methyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide

6) N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-(R or S)-10-cyclopropylmethyl-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide

7) N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-(R or S)-10-benzyl-4-hydroxy-2-oxo-2H-cycloocta[b] pyran-3-yl)methyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide

PREPARATION 6

(3-Benzaldehyde)-carbamic acid, phenylmethyl ester (Formula B-2) Refer to Chart B

A flask with a nitrogen inlet is charged with sodium bicarbonate (10.4 g) in 200 mL of THF and 200 mL of water, and m-aminobenzaldehyde of formula B-1 (10.0 g) and benzyl chloroformate (13.6 mL) are added sequentially. The mixture is stirred at room temperature for 40 min. Ether is then added, and the organic layer is separated, washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to give a brown oil. Column chromatography on 300 g of silica gel yields 16.3 g of the title compound as a pale yellow oil. An analytical sample is crystallized from ethyl acetate-hexane.

Physical characteristics are as follows:

MP 100°–104° C.

^{1}H NMR ($CDCl_3$) δ9.98, 7.91, 7.69, 7.59, 7.43–7.35, 6.83, 5.23 ppm.

^{13}C NMR ($CDCl_3$) δ191.8, 153.0, 138.6, 137.1, 135.6, 129.7, 128.6, 128.4, 128.3, 124.6, 124.2, 119.1, 67.2 ppm.

IR (mineral oil) 3269, 2954, 2925, 2868, 2855, 1729, 1682, 1597, 1560, 1465, 1455, 1326, 1294, 1237, 1229, 1170, 1155, 1048, 695 cm-1.

Elemental analysis, found: C, 70.74; H, 5.14; N, 5.33.

MS (EI) m/e 255, 211, 91.

For high resolution, found 255.0900.

PREPARATION 7

[3-(1-Hydroxy-3-methylbutyl)phenyl]-carbamic acid, phenylmethyl ester (Formula B-3 wherein R_1 is isobutyl) Refer to Chart B

A flask with a nitrogen inlet is charged with the title compound of Preparation 6 (4.0 g) and 60 mL of dry tetrahydrofuran. The mixture is cooled to 0° C., and isobutyl magnesium chloride (17.2 mL) is added. The reaction mixture is then allowed to warm to room temperature and stir for 2 hours. Saturated ammonium chloride is added to quench the reaction, and the mixture is partitioned between ether and water. The organic layer is washed with water and concentrated to give 5.78 g of pale yellow oil. The crude material is crystallized from ethyl acetate-hexane to yield 4.13 g of the title compound as white crystals.

Physical characteristics are as follows:

MP 73°–77° C.

^{1}H NMR ($CDCl_3$) δ7.41–7.33, 7.25, 7.05, 6.74, 5.19, 4.73–4.65, 1.91, 1.73–1.65, 1.47, 0.93 ppm.

IR (Nujol) 3400, 3249, 3085, 2953, 2925, 2869, 2855, 1697, 1615, 1602, 1563, 1450, 1283, 1245, 1177, 1067, 1017, 798, 773, 740, 696 cm^{-1}.

Elemental analysis, found: C, 72.58; H, 7.25; N, 4.55.

MS (El) m/z 313, 257, 213, 91.

PREPARATION 8

[3-[1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl-carbamic acid, phenylmethyl ester (Formula B-5 wherein R_1 is isobutyl) Refer to Chart B

A 200-mL, three-necked flask with a Dien-Stark trap and a nitrogen inlet is charged with p-toluenesulfonic acid (0.66 g) and toluene (100 mL) and warmed to reflux to collect 20 mL in the Dien-Stark trap. The reaction mixture is cooled to room temperature, and the trap is emptied. 4-Hydroxy-2H-cycloocta[b]pyran-2-one of formula B-4 (2.48 g) and the title compound of Preparation 7 (4.0 g) are added to the reaction mixture and then heated to reflux for 6.5 h. The reaction mixture is allowed to stand at room temperature overnight, then poured into 350 mL of ethyl acetate, washed with two 25-mL portions of water, 25 mL of saturated sodium bicarbonate, and 25 mL of water. The organic layer is concentrated to give 7.9 g of yellow oil. Column chromatography on 150 g of silica gel (elution with 10–50%

ethyl acetate in hexane) gives 0.217 g of the title product as an off-white foam.

Physical characteristics are as follows:

MP 73°–78° C. (decomposition).

^{1}H NMR ($CDCl_3$) δ7.38–7.25, 7.13, 6.72, 6.01, 5.19, 4.48, 2.58, 2.41, 1.93, 1.74, 1.62–1.33, 0.96 ppm.

PREPARATION 9

(R or S)-[3-[1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl]-carbamic acid, phenylmethyl ester (Formula B-5 wherein R_1 is isobutyl) Refer to Chart B

A stock solution of the title compound of Preparation 8 (32 mg/mL) in 30% isopropyl alcohol and 0.1% acetic acid in hexane is chromatographed on a 2.0×25 cm (R, R) Whelk-O 1 column at 2 mL per injection using an automated chromatographic system. The eluant is monitored at 310 nm, the flow rate was 10 mL/min and appropriate fractions from multiple injections combined and concentrated in vacuo to give snowy white solids.

Physical characteristics are as follows:

The retention time of the title compound is 18.8 min.

PREPARATION 10

(R or S)-[3-[1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl]-carbamic acid, phenylmethyl ester (Formula B-5 wherein R_1 is isobutyl) Refer to Chart B

The title compound of Preparation 8 is separated as described in Preparation 9 above.

Physical characteristics are as follows:

The retention time of the title compound is 22.1 min.

PREPARATION 11

(R or S)-3-[1-(3-Aminophenyl)-3-methylbutyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyranone (Formula B-6 wherein R_1 is isobutyl) Refer to Chart B

A flask with a nitrogen inlet is charged with a solution of the title compound of Preparation 9 (0.637 g) in 6 mL of ethanol. Cyclohexene (6 mL) and 10% palladium on carbon (0.16 g) are added, and the reaction mixture is heated at reflux for 2 h. The mixture is then filtered through Celite and concentrated to give 0.205 g of the title compound as an off-white foam.

Physical characteristics are as follows:

MP 158°–162° C.

MS (EI) m/z 355, 312, 299, 161, 106

For high resolution, found: 355.2144.

EXAMPLE 8

(R or S)-N-[3-1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl]1-methyl-1H-imidazole-4-sulfonamide (Formula B-7 wherein R_1 is isobutyl and R_2 is 1-methylimidazole) Refer to Chart B.

A flask with a nitrogen inlet is charged with the title compound of Preparation 11 (0.095 g), 1-methylimidazole-4-sulfonyl chloride (0.048 g), and 5 mL of methylene chloride (CH_2Cl_2). Pyridine (0.53 mL) is added, and the reaction mixture is stirred at room temperature for ca. 18 h. A precipitate forms, which is filtered to give 0.097 g of a white solid. Recrystallization from methanol-chloroform yields 0.065 g of the title compound as a white powder.

Physical characteristics are as follows:

MP 207°–210° C.

^{1}H NMR ($CDCl_3$) δ10.4, 10.0, 7.70, 7.11, 7.05, 6.92, 4.21, 3.64, 2.54, 2.16, 1.62, 1.53, 1.43, 1.34, 0.85 ppm.

MS (EI) m/z 499, 456, 443, 306, 251, 160, 145

For high resolution, found: 499.2151

PREPARATION 12

(R or S)-3-[1-(3-Aminophenyl)-3-methylbutyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyranone (Formula B-6 wherein R_1 is isobutyl) Refer to Chart B

Following the general procedure of Preparation 11, and making non-critical variations, but substituting the title product of Preparation 10 for the title product of Preparation 9, 0.189 g of the title compound is obtained as a grey solid.

Physical characteristics are as follows:

MS (EI) m/z 355, 312, 299, 161

For high resolution, found: 355.2135

EXAMPLE 9

(R or S)-N-[3-1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula B-7 wherein R_1 is isobutyl and R_2 is 1-methylimidazole) Refer to Chart B

Following the general procedure of Example 8, and making non-critical variations, but substituting the title product of Preparation 12 for the title product of Preparation 11, 0.047 g of the title compound is obtained as a white solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ10.45, 10.06, 7.70, 7.11, 7.05, 6.94, 4.21, 3.64, 2.55, 2.16, 1.62, 1.53, 1.42, 1.35, 0.86 ppm.

MS (EI) m/z 499, 456, 443, 354, 306, 160, 145

For high resolution, found: 499.2146

PREPARATION 13

[3-(Cyclopropyl-hydroxymethyl)-phenyl]-methanol (Formula C-2) Refer to Chart C

To a solution of 6.5 mL of 3-bromobenzylalcohol of formula C-1 in 900 mL of tetrahydrofuran under nitrogen at −78° C. is added 46 mL of a 1.4M solution of methyllithium in diethyl ether. The solution is stirred for 20 min and then 66 mL of a 1.6M solution of n-butyllithium in hexane is added. The solution is stirred 25 min and then 6 mL of cyclopropanecarboxaldehyde is added. The solution is stirred 1.5 h, warmed to 0° C. and stirred for 40 min. Next the solution is warmed to room temperature and stirred for 30 min. Finally the solution is heated at reflux for 1 h. The solution is poured onto 800 mL of water and acidified with concentrated HCl followed by 5% aqueous HCl to adjust the pH to approximately 6. The layers are separated and the aqueous extracted with two portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated to afford a yellow oil which is chromatographed over 900 g 230–400 mesh silica gel (2:1 ethyl acetate:hexane) to afford a 6.61 g (68%) of the desired alcohol as a yellow oil.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.41–7.26, 4.67, 3.99–3.96, 2.18, 1.28–1.14, 0.68

PREPARATION 14

3-[cyclopropyl [3-[hydroxymethyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one (Formula C-3) Refer to Chart C

To a solution of 501 mg of the title product of Preparation 13 in 50 mL of dichloromethane in the presence of molecular sieves 3A under nitrogen is added 492 mg of 4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[b]pyran-2-one followed by 49 mg of p-toluenesulfonic acid monohydrate. The solution is heated at reflux for 2 h and then an additional 105 mg p-toluenesulfonic acid monohydrate is added and heating continued for a further hour. The solution is concentrated in vacuo to afford a white foam which is treated with water and then 1N KOH and extracted with one portion of ethyl acetate. The organic layer is washed with one portion of 1N

KOH. The combined aqueous layers are acidified with 5% aqueous HCl and extracted with three portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated in vacuo to afford a yellow oil which is chromatographed over 180 g of 230–400 mesh silica gel (2:1 ethyl acetate:hexane) to afford 436 mg of the desired benzyl alcohol as a white foam.

Physical characteristics are as follows:

MP 65°–70° C.

^{1}H NMR ($CDCl_3$) δ7.25–7.03, 4.36, 3.70–3.67, 2.41–2.37, 2.24–2.23, 1.53–1.50, 1.35–1.05, 0.54–0.43, 0.42–0.21, 0.07–0.02.

PREPARATION 15

3-[Cyclopropyl [3-[bromomethyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one; and 3-[cyclopropyl[3-[chloromethyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one (Formulas C-4,5) Refer to Chart C

To a solution of 1.01 g of the title product of Preparation 14 in 70 mL of dichloromethane under nitrogen at 0° C. is added 2.00 g of triphenylphosphine and 2.58 g of carbon tetrabromide in sequence. The solution is stirred 1 h and then poured onto brine. The layers are separated and the aqueous extracted with three portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated to afford a yellow oil which is triturated with ether. The solid is filtered off and the filtrate concentrated and chromatographed over 180 g of 230–400 mesh silica gel (1:1 hexane:ethyl acetate) to afford 374 mg of the desired title product as a mixture of bromide and chloride. The solids isolated from the filtration are chromatographed as above to afford an additional 699 mg of the title product as a mixture of bromide and chloride.

Physical characteristics are as follows:

Mass Spectrum m/e 418, 416 (M^+ for Br), 388, 374, 372 (M^+ for Cl), 337, 246, 233, 220, 207, 195, 179, 153, 143, 129.

PREPARATION 16

3-[Cyclopropyl[3-[(phenylthio)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-Cycloocta[b]pyran-2-one (Formula C-6) Refer to Chart C

To a solution of 138 mg of the title products of Preparation 15 in 5 mL of dichloromethane is added 0.04 mL of thiolphenol and 0.17 mL of diisopropylethylamine in sequence. The solution is heated at reflux for 1 h and then allowed to stand at room temperature overnight. The solution is poured onto brine and treated with 5% aqueous hydrochloric acid. The layers are separated and the aqueous extracted with three portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated to afford a yellow oil which is chromatographed over 80 g of 230–400 mesh silica gel (2:1 hexane:ethyl acetate) to afford 111 mg of the desired sulfide as a white foam.

Physical characteristics are as follows:

MP 137°–139° C.

Mass Spectrum m/e 446 (M^+), 418, 337, 295, 233, 220, 207, 185, 145, 128, 109, 91, 79, 55, 40.

EXAMPLE 10

3-[Cyclopropyl[3-[(phenylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-Cycloocta[b]pyran-2-one (Formula C-7) Refer to Chart C

To a solution of 119 mg of the title product of Preparation 16 in 5 mL of tetrahydrofuran and 5 mL of methanol at 0° C. is added a solution of 279 mg of oxone in 5 mL of water. The solution is stirred 2.5 h and then warmed to room temperature and stirred 2 h. The solution is filtered and the solids washed with chloroform. The filtrate is diluted with water and the layers are separated. The aqueous is extracted with three portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated to afford a clear oil which is chromatographed over 80 g of 230–400 mesh silica gel (1:1 hexane:ethyl acetate) to afford 78 mg of the title product as a white foam.

Physical characteristics are as follows:

MP 80°–85° C.

Mass Spectrum m/e 479 (M^++1), 463, 450, 391, 337, 309, 207, 161, 149, 127, 115, 71, 57, 41.

Exact mass found: 479.1885.

EXAMPLES 11–39

The following compounds of the present invention are prepared by an analogous synthetic route to that described above:

11) 3-[cyclopropyl[3-[(4-cyanophenylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

The starting material, 4-cyanobenzenethiol, is prepared from 4-cyanobenzenesulfonyl chloride according to a general literature procedure: Wagner, A. W. Ber Deutsch Chem Ges, 99:375 (1966).

Physical characteristics are as follows:

MP 100°–105° C.

Mass Spectrum m/e 504 (M^++1), 337, 247, 207, 143.

Exact mass found 504.1843.

12) 3-[cyclopropyl[3-[(4-fluorophenylsulfonyl)methyl]phenyl]methyl]- 5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

Physical characteristics are as follows:

MP 95°–100° C.

^{1}H NMR ($CDCl_3$) δ7.61–7.57, 7.40–7.37, 7.27–7.20, 7.13–7.07, 7.02–6.99, 6.42, 4.30, 3.88–3.85, 2.64–2.61, 2.51–2.47, 1.83–1.40, 1.40–1.27, 0.69–0.58, 0.48–0.43, 0.19–0.14.

13) 3-[cyclopropyl[3-[(4-methylphenylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

Physical characteristics are as follows:

MP 100°–105° C.

^{1}H NMR ($CDCl_3$) δ7.37–7.34, 7.25–7.22, 7.17–7.05, 6.86–6.84, 4.15, 3.60–3.58, 2.52–2.42, 2.42–2.30, 2.28, 1.70–1.14, 0.57–0.32, 0.32–0.20, 0.06-(–)0.16.

14) 3-[cyclopropyl[3-[(4-carboxyphenylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

Physical characteristics are as follows:

MP 90°–95° C.

Mass Spectrum m/e 523 (M^++1), 337, 247, 207, 143.

Exact mass found 523.1785.

15) 3-[cyclopropyl[3-[(2-(1-methylimidazoyl)sulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

Physical characteristics are as follows:

MP 95°–103° C.

^{1}H NMR ($CDCl_3$) δ7.36–7.34, 7.29–7.27, 7.14, 7.06–7.03, 6.98 (s, 1H), 6.86, 4.30, 3.73–3.70, 3.20, 2.67–2.54, 1.90–1.36, 0.71–0.50, 0.46–0.33, 0.18–0.03.

16) 3-[cyclopropyl[3-[(2-pyrimidinylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

17) 3-[cyclopropyl[3-[(2-pyridinylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

18) 3-[cyclopropyl[3-[(1-methyl-4-imidazolylsulfonyl) methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

19) 3-[cyclopropyl[3-[(5-cyano-2-pyridinylsulfonyl) methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

20) 3-[cyclopropyl[3-[(2-benzimidazolylsulfonyl) methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

21) 3-[cyclopropyl[3-[(2-quinolinylsulfonyl)methyl] phenyl]methyl]- 5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

22) 3-[cyclopropyl[3-[(4-cyanophenylsulfonyl)methyl] phenyl]methyl]-4-hydroxy-coumarin

23) 3-[cyclopropyl[3-[(2-pyridinylsulfonyl)methyl] phenyl]methyl]-4-hydroxy-coumarin

24) 3-[cyclopropyl[3-[(1-methyl-4-imidazolylsulfonyl) methyl]phenyl]methyl]-4-hydroxy-coumarin

25) 3-[cyclopropyl[3-[(5-cyano-2-pyridinylsulfonyl) methyl]phenyl]methyl]-4-hydroxy-coumarin

26) 3-[cyclopropyl[3-[(2-benzimidazolylsulfonyl) methyl]phenyl]methyl]-4-hydroxy-coumarin

27) 3-[cyclopropyl[3-[(2-quinolinylsulfonyl)methyl] phenyl]methyl]-4-hydroxy-coumarin

28) 3-[cyclopropyl[3-[(4-cyanophenylsulfonyl)methyl] phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl) propyl]-2H-pyran-2-one

29) 3-[cyclopropyl[3-[(2-pyridinylsulfonyl)methyl] phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl) propyl]-2H-pyran-2-one

30) 3-[cyclopropyl[3-[(1-methyl-4-imidazolylsulfonyl) methyl]phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one

31) 3-[cyclopropyl[3-[(5-cyano-2-pyridinylsulfonyl) methyl]phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one

32) 3-[cyclopropyl[3-[(2-benzimidazolylsulfonyl) methyl]phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one

33) 3-[cyclopropyl[3-[(2-quinolinylsulfonyl)methyl] phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl) propyl]-2H-pyran-2-one

34) 3-[cyclopropyl[3-[(4-cyanophenylsulfonyl)methyl] phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

35) 3-[cyclopropyl[3-[(2-pyridinylsulfonyl)methyl] phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

36) 3-[cyclopropyl[3-[(1-methyl-4-imidazolylsulfonyl) methyl]phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

37) 3-[cyclopropyl[3-[(5-cyano-2-pyridinylsulfonyl) methyl]phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

38) 3-[cyclopropyl[3-[(2-benzimidazolylsulfonyl) methyl]phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

39) 3-[cyclopropyl[3-[(2-quinolinylsulfonyl)methyl] phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

PREPARATION 17

5,6-Dihydro-4-Hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one (Formula D-1: R_1 is phenethyl, R_2 is propyl) Refer to Chart D

Methyl acetoacetate (1.47 mL) is added to a suspension of sodium hydride (567 mg, 60% dispersion in mineral oil) in THF (30 mL) at 0° C. After 15 minutes, n-butyl lithium (8.5 mL, 1.6M solution in hexane) is added dropwise and the reaction is stirred 15 minutes. 1-Phenyl-3-hexanone (2.0 g) is then added via syringe all at once to the reaction mixture. The reaction is stirred an additional hour, then poured into a saturated ammonium chloride solution. It is extracted with EtOAc, dried over anhydrous sodium sulfate and evaporated in vacuo. The material obtained is dissolved in THF (25 mL) and a 0.1N sodium hydroxide (113 mL) solution is added. After stirring three hours, the mixture is extracted with ethyl acetate (1×). The aqueous layer is adjusted to pH 3 with hydrochloric acid, then extracted with CH_2Cl_2 (3×25 mL), dried over anhydrous magnesium sulfate and evaporated to afford the title product as a white solid.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, $CDCl_3$): δ0.96, 1.21, 1.48, 1.72, 1.98, 2.73, 3.43, 7.15–7.32.

Anal. Found: C, 73.77; H, 7.96.

PREPARATION 18

4-Hydroxy-3-[1-(3-nitrophenyl)-propyl]-5,6-dihydro-6-phenethyl-6-propyl-2H-pyran-2-one (Formula D-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) Refer to Chart D

To a solution of the title product of Preparation 17 (Formula D-1: R_1 is phenethyl, R_2 is propyl) (1 g) and 3-nitrobenzaldehyde (Formula D-2) (581 mg) in dry THF at 0° C. is added $AlCl_3$ (1.0 g) as one solid portion. The cooling bath is removed and the yellow solution is allowed to stir at room temperature for 2 hrs. The reaction mixture is quenched by the addition of solid Na_2CO_3-$10H_2O$ (2.2 g) and vigorously stirred for 5 min. The mixture is filtered through celite with ether and the filtrate is evaporated to dryness in vacuo. The benzylidene intermediate of the formula D-3 and CuBr—Me_2S (237 mg) are dissolved in dry THF and a solution of Et_3Al (4.23 mL; 1M in hexane) is added at room temperature, dropwise over 5 min. When the reaction is complete (as determined by tlc), it is quenched by the addition of water and the reaction mixture is transferred to a separatory funnel with ether. The aqueous layer is extracted with ether (3×15 mL) and the combined organic layers are washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo to provide an oil. Flash chromatography on silica gel with Hexanes/EtOAc (3:1) provides 1.1 g of the title product as a light yellow foam.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers.

^{1}H NMR (300 MHz, CD_3OD) δ0.93, 1.37, 1.74, 1.82–2.14, 2.29, 2.52–2.71, 4.19, 6.98–7.24, 7.44, 7.72, 8.02, 8.26.

PREPARATION 19

3-[Cyclopropyl-(3-nitrophenyl)-methyl]-4-hydroxy-5,6-dihydro-6-phenethyl-6-propyl-2H-pyran-2-one (Formula D-4: R_1 is phenethyl, R_2 is propyl, R_3 is cyclopropyl) Refer to Chart D

To a solution of the title product of Preparation 17 (Formula D-1: R_1 is phenethyl, R_2 is propyl) (1 g) and 3-nitrobenzaldehyde (Formula D-2) (581 mg) in dry THF at 0° C. is added $AlCl_3$ (1.0 g) as one solid portion. The cooling bath is removed and the yellow solution is allowed to stir at room temperature for 2 hrs. The reaction mixture is quenched by the addition of solid Na_2CO_3-$10H_2O$ (2.2 g) and vigorously stirred for 5 min. The mixture is filtered through celite with ether and the filtrate is evaporated to dryness in vacuo. The benzylidene intermediate of formula D-3 and CuBr—Me_2S (237 mg) are dissolved in dry THF

and cooled to −78° C. A solution of cyclopropylmagnesium bromide (15.6 mL; 0.25M in THF) is added dropwise over 10 min and the reaction mixture is stirred for 30 min. The reaction is quenched by the addition of water and neutralized by the addition of 1N HCl. The reaction mixture is transferred to a separatory funnel with ether and the aqueous layer is extracted with ether (3×15 mL). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered and evaporated in vacuo to provide an oil. Flash chromatography on silica gel with Hexanes/EtOAc (3:1) provides 0.9 g of the title product as a light yellow foam.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers.

^{1}H NMR (300 MHz, CD_3OD) δ0.25, 0.53, 0.74, 0.94, 1.41, 1.68–2.13, 2.57–2.72, 3.38, 7.04–7.23, 7.46, 7.82, 8.03, 8.30.

PREPARATION 20

3-[1-(3-Aminophenyl)-propyl]-4-hydroxy-5,6-dihydro-6-phenethyl-6-propyl-2H-pyran-2-one (Formula D-5: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) Refer to Chart D

To a solution of the title product of Preparation 18 (Formula D-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) (350 mg) in MeOH at room temperature is added 10% Pd/C (35 mg) and ammonium formate (521 mg). The resulting mixture is stirred for 2 hrs. and then filtered through celite with CH_2Cl_2. The filtrate is evaporated in vacuo and the residue is triturated with CH_2Cl_2 (3×10 mL). The combined organic solution is filtered and evaporated in vacuo to provide the 325 mg of the title compound as a light yellow foam.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ0.89, 1.40, 1.64–2.07, 2.20, 2.62, 3.94, 6.54, 6.72–7.25.

The compounds of formula D-5, wherein R_1 is propyl, R_2 is propyl and R_3 is ethyl or t-butyl are prepared by analogous procedures.

Physical characteristics of the compound of the formula D-5, wherein R_1 is and R_2 are propyl and R_3 is ethyl, are as follows:

^{1}H NMR: 0.9, 1.3, 1.5–1.8, 2.0, 2.2, 2.5, 3.9, 4.5, 6.5, 6.8, 7.0 ppm

TLC R_f: 0.32 (10% ethyl acetate in dichloromethane).

EXAMPLE 40

4-Cyano-N-[3-[1-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 4-cyanophenyl) Refer to Chart D

To a solution of the title product of Preparation 20 (Formula D-5: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) (30 mg) and 4-cyanobenzenesulfonyl chloride of formula D-7, wherein R_4 is cyanophenyl, (16.1 mg) in CH_2Cl_2 (1 mL) at room temperature is added pyridine (13 μL) via syringe. The resulting solution is stirred for 3 hrs, after which the starting amine is consumed. The mixture is flash chromatographed on silica gel with the 5% EtOAc in CH_2Cl_2 to provide 21 mg of the title product as a white foam.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ0.6–1.1, 1.2–2.2, 2.4–2.7, 3.86–4.01, 6.89–7.45, 7.66–7.92.

HRMS found: 559.2267.

EXAMPLE 41

N-[3-[1-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5; R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as an off-white amorphous solid after flash chromatography with 4% MeOH/EtOAc.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers and tautomerism.

^{1}H NMR (300 MHz, $CDCl_3$) δ0.75–0.96, 1.17–1.43, 1.45–2.11, 2.43–2.68, 3.24, 3.64, 3.94, 6.72–7.51.

HRMS found: 538.2383.

EXAMPLE 42

N-[3-[1-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-8-quinolinesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is quinolin-8-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) and 8-quinolinesulfonyl chloride of formula D-7 wherein 4_4 is quinolin-8-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers and tautomerism.

^{1}H NMR (300 MHz, $CDCl_3$) δ0.66, 0.90, 1.17–1.44, 1.58–2.03, 2.38–2.64, 3.77, 6.68–7.27, 7.35–7.69, 8.02, 8.26, 9.14.

HRMS found: 585.2402.

EXAMPLE 43

N-[3-[1-(4-hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-8-quinolinesulfonamide (Formula D-6: R_1 is R_2 is propyl, R_3 is ethyl, R_4 is quinolin-8-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is ethyl) and 8-quinolinesulfonyl chloride of formula D-7 wherein R_4 is quinolin-8-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers and tautomerism.

^{1}H NMR (300 MHz, CD_3OD) δ0.67, 0.85, 1.27, 1.54, 2.01, 3.73, 6.78, 6.90, 7.04, 7.57, 8.12, 8.29, 8.38, 9.13.

HRMS found: 523.2276.

Anal. found: C, 66.09; H, 6.60; N, 5.13.

EXAMPLE 44

N-[3-[1-(4-hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazolesulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is ethyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl, using the general procedure for sulfonylation of Example 40 to yield

the title compound as an off-white amorphous solid after flash chromatography with 4% MeOH/EtOAc.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ0.88, 1.32, 1.64, 1.93, 2.16, 2.56, 3.68, 3.91, 6.87, 7.03, 7.14, 7.53, 7.64.

HRMS found: 476.2223.

EXAMPLE 45

4-Fluoro-N-[3-[1-(4-hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is ethyl, R_4 is 4-fluorophenyl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is ethyl) and 4-fluoro-benzenesulfonyl chloride of formula D-7 wherein R_4 is 4-fluorophenyl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers and tautomerism.

^{1}H NMR (300 MHz, $CDCL_3$) δ0.51–1.03, 1.15–1.73, 1.81–2.48, 2.73, 3.91, 6.69, 6.88, 7.09, 7.78.

HRMS found: 490.2085.

EXAMPLE 46

4-Cyano-N-[3-[1-(4-hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is ethyl, R_4 is 4-cyanophenyl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is ethyl) and 4-cyano-benzenesulfonyl chloride of formula D-7 wherein R_4 is 4-cyanophenyl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers and tautomerism.

^{1}H NMR (300 MHz, $CDCl_3$) δ0.68–0.96, 1.15–1.42, 1.44–1.76, 1.83–2.12, 3.18, 3.88, 6.69–7.18, 7.71, 7.85.

HRMS found: 497.2126.

EXAMPLE 47

N-[3-[1-(4-hydroxy-6,6-diisobutyl-2-oxo-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is isobutyl, R_2 is isobutyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is propyl, R_2 is isobutyl, R_3 is ethyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as an off-white amorphous solid after flash chromatography with 4% MeOH/EtOAc.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ0.82–0.94, 1.52–1.83, 1.86–2.03, 2.06–2.22, 2.60, 3.68, 3.92, 6.87, 7.03, 7.16, 7.56, 7.65.

HRMS found: 504.2531.

Anal. found: C, 62.03; H, 7.43; N, 8.20.

EXAMPLE 48

N-[3-[1-(4-hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-1-methyl-1H-imidazolesulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as an off-white amorphous solid after flash chromatography with 4% MeOH/EtOAc.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ0.12, 0.43, 0.68, 0.90–0.97, 1.36, 1.71, 2.60, 3.12, 3.67, 6.88, 7.06, 7.24, 7.51, 7.65.

HRMS found: 488.2225.

Anal. found: C, 61.25; H, 6.94; N, 8.42.

EXAMPLE 49

N-[3-[1-(4-Hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-8-quinolinesulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is quinolin-8-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl) and 8-quinolinesulfonyl chloride of formula D-7 wherein R_4 is quinolin-8-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ–0.14, 0.01, 0.35, 0.89, 1.35, 1.63, 2.52, 2.94, 6.79, 6.94, 7.09, 7.64, 8.12, 8.28, 8.41, 9.13.

HRMS found: 535.2256

Anal. found: C, 67.58; H, 6.53; N, 5.11.

EXAMPLE 50

4-Cyano-N-[3-[1-(4-hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is 4-cyanophenyl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl) and 4-cyano-benzenesulfonyl chloride of formula D-7 wherein R_4 is 4-cyanophenyl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ0.13, 0.44, 0.62, 0.91, 1.19, 1.67, 2.57, 3.14, 6.80, 7.12, 7.25, 7.83.

HRMS found: 509.2096

Anal. found: C, 65.86; H, 6.39; N, 5.48.

EXAMPLE 51

4-Fluoro-N-[3-[1-(4-hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is 4-fluorophenyl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl) and 4-fluoro-benzenesulfonyl chloride of formula D-7 wherein R_4 is 4-fluorophenyl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ0.11, 0.43, 0.62, 0.92, 1.34, 1.65, 2.57, 3.13, 6.79, 7.03–7.24, 7.75.

HRMS found: 502.2063.

Anal. found: C, 63.96; H, 6.29; N, 2.71.

PREPARATION 21

Chiral HPLC resolution of 4-Hydroxy-3-[1-(3-nitrophenyl)-propyl]-5,6-dihydro-6,6-dipropyl-2H-pyran-2-one (Formula D-4: R_1 is propyl, R_2 is propyl, R_3 is ethyl) Refer to Chart D

A solution of the title product of Preparation 18 (Formula D-4: R_1 is propyl, R_2 is propyl, R_3 is ethyl) (30 mg/mL) in 15% isopropyl alcohol in hexane is chromatographed on a 2.0×25 cm (R,R) Whelk-O 1 (Regis technologies, Inc., Morton Grove, Ill. 60053) column at 1 mL per injection using an automated chromatographic system. The eluant is monitored at 270 nM and appropriate fractions from multiple injections combined and concentrated in vacuo to give tan oils. Fractions from multiple injections are analyzed on a 0.46×25 cm (S,S) Whelk-O 1 column with the same solvent at 1.0 mL/min. The first peak from the 1.0 cm column is >99% ee (Rt is min) and the latter peak is 92% ee (Rt is min). Prior to further use, the resolved materials are subjected to flash chromatography on silica gel with 3:1 hexanes/EtOAc. The resolved materials are converted to the amines of Formula D-5 using the conditions described in Preparation 20.

Physical characteristics are as follows:

The resolved materials were found to exhibit identical ^{1}H NMR and tlc behavior as the racemic material.

EXAMPLE 52

(R or S)-N-[3-[1-(4-Hydroxy-2-oxo-6,6-dipropyl-6,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-8-quinolinesulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is ethyl, R_4 is quinolin-8-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 21 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is ethyl) and 8-quinolinesulfonyl chloride of formula D-7 wherein R_4 is quinolin-8-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR and tlc behavior is identical to that of racemic mixture.

^{1}H NMR (300 MHz, CD_3OD) δ0.67, 0.85, 1.27, 1.54, 2.01, 3.73, 6.78, 6.90, 7.04, 7.57, 8.12, 8.29, 8.38, 9.13.

MS m/e (rel%): 523 (100), 524 (34), 129 (11), 525 (11), 522 (10), 130 (7), 139 (5), 134 (4).

EXAMPLE 53

(R or S)-N-[3-[1-(4-hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 21 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is ethyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as an off-white amorphous solid after flash chromatography with 4% MeOH/EtOAc.

Physical characteristics are as follows:

^{1}H NMR and tlc behavior is identical to racemic mixture.

^{1}H NMR (300 MHz, CD_3OD) δ0.88, 1.32, 1.64, 1.93, 2.16, 2.56, 3.68, 3.91, 6.87, 7.03, 7.14, 7.53, 7.64.

MS m/e (rel%): 476 (100), 477 (28), 139 (14), 492 (12), 134 (11), 278 (10), 478 (10), 83 (9), 552 (8), 145 (7).

EXAMPLE 54

(S or R)-N-[3-[1-(4-Hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-8-quinolinesulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is ethyl, R_4 is quinolin-8-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 21 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is ethyl) and 8-quinolinesulfonyl chloride of formula D-7 wherein R_4 is quinolin-8-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR and tlc behavior is identical to that of racemic mixture.

^{1}H NMR (300 MHz, CD_3OD) δ0.67, 0.85, 1.27, 1.54, 2.01, 3.73, 6.78, 6.90, 7.04, 7.57, 8.12, 8.29, 8.38, 9.13.

MS m/e (rel%): 523 (100), 524 (34), 522 (24), 539 (13), 525 (10), 129 (10), 130 (5), 134 (5), 128 (5), 540 (5).

EXAMPLE 55

(S or R)-N-[3-[1-(4-hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 21 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is ethyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as an off-white amorphous solid after flash chromatography with 4% MeOH/EtOAc.

Physical characteristics are as follows:

^{1}H NMR and tlc behavior is identical to racemic mixture.

^{1}H NMR (300 MHz, CD_3OD) δ0.88, 1.32, 1.64, 1.93, 2.16, 2.56, 3.68, 3.91, 6.87, 7.03, 7.14, 7.53, 7.64.

MS m/e (rel%): 476 (100), 477 (28), 139 (19), 490 (15), 498 (14), 83 (12), 478 (9), 55 (9), 145 (9), 134 (7).

EXAMPLE 56

(R or S)-N-[3-[1-(4-Hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 21 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as an off-white amorphous solid after flash chromatography with 4% MeOH/EtOAc.

Physical characteristics are as follows:

^{1}H NMR and tlc behavior is identical to racemic mixture.

^{1}H NMR (300 MHz, CD_3OD) δ0.12, 0.43, 0.68, 0.90–0.97, 1.36, 1.71, 2.60, 3.12, 3.67, 6.88, 7.06, 7.24, 7.51, 7.65.

MS m/e (rel%): 488 (100), 489 (30), 139 (18), 145 (14), 490 (10), 55 (10), 83 (9), 564 (7), 146 (7), 510 (7).

EXAMPLE 57

(S or R)-N-[3-[1-(4-Hydroxy-2-oxo-6,6-dipropyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is

propyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine Preparation 21 (Formula D-5: R_1 is propyl, R_2 is propyl, R_3 is cyclopropyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as an off-white amorphous solid after flash chromatography with 4% MeOH/EtOAc.

Physical characteristics are as follows:

^{1}H NMR and tlc behavior is identical to racemic mixture.

^{1}H NMR (300 MHz, CD_3OD) δ0.12, 0.43, 0.68, 0.90–0.97, 1.36, 1.71, 2.60, 3.12, 3.67, 6.88, 7.06, 7.24, 7.51, 7.65.

MS m/e (rel%): 488 (100), 489 (29), 139 (18), 145 (16), 83 (10), 55 (10), 490 (10), 510 (8), 146 (8), 144 (7).

EXAMPLE 58

4-Cyano-N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is 4-cyanophenyl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is phenethyl, R_2 is propyl, R_3 is cyclopropyl) and 4-fluoro-benzenesulfonyl chloride of formula D-7 wherein R_4 is 4-cyanophenyl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ0.11, 0.42, 0.61, 0.95, 1.24, 1.74–2.00, 2.61–2.73, 3.30, 6.83–7.23, 7.71–7.84.

HRMS found: 571.2267

EXAMPLE 59

4-Fluoro-N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is 4-fluorophenyl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is phenethyl, R_2 is propyl, R_3 is cyclopropyl) and 4-fluoro-benzenesulfonyl chloride of formula D-7 wherein R_4 is 4-fluorophenyl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers.

^{1}H NMR (300 MHz, CD_3OD) δ0.11, 0.43, 0.67, 0.96, 1.41, 1.67–2.13, 2.62, 3.16, 6.84, 7.02–7.31, 7.72.

HRMS found: 564.2211.

EXAMPLE 60

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-8-quinolinesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is quinolin-8-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is phenethyl, R_2 is propyl, R_3 is cyclopropyl) and 8-quinolinesulfonyl chloride of formula D-7 wherein R_4 is quinolin-8-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers.

^{1}H NMR (300 MHz, CD_3OD) δ–0.13, 0.01, 0.35, 0.93, 1.46, 1.54, 1.58–2.06, 2.56, 2.96, 6.81–7.23, 7.50–7.68, 8.08, 8.24, 8.37, 9.12.

HRMS found: 597.2398

EXAMPLE 61

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is cyclopropyl, R_4 is 1-methyl-imidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is phenethyl, R_2 is propyl, R_3 is cyclopropyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers.

^{1}H NMR (300 MHz, CD_3OD) δ0.13, 0.42, 0.67, 0.95, 1.44, 1.68–2.13, 2.56, 3.17, 6.91, 7.01–7.33, 7.52, 7.63.

HRMS found: 550.2370.

EXAMPLE 62

N-[3-[1-(4-Hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-cyclopropylmethyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is cyclopropyl, R_4 is 1-methyl-imidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is phenethyl, R_2 is phenethyl, R_3 is cyclopropyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazol-4-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ0.13, 0.42, 0.68, 1.73, 1.88–2.17, 2.68, 3.19, 3.64, 6.93, 7.02–7.31, 7.52, 7.64.

HRMS found: 612.2530.

EXAMPLE 63

N-[3-[1-(4-Hydroxy-2-oxo-6,6-dipentyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is pentyl, R_2 is pentyl, R_3 is ethyl, R_4 is 1-methyl-imidazol-4-yl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is pentyl, R_2 is pentyl, R_3 is ethyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 1-methylimidazole-4-yl, using the general procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ0.87, 1.25, 1.55–1.68, 1.92, 2.13, 2.57, 3.66, 3.93, 6.86, 7.03, 7.16, 7.55, 7.63.

EXAMPLE 64

4-Cyano-N-[3-[1-(4-Hydroxy-2-oxo-6,6-dipentyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is pentyl, R_2 is pentyl, R_3 is ethyl, R_4 is 4-cyanophenyl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is pentyl, R_2 is pentyl, R_3 is ethyl) and 1-methyl-imidazole-4-sulfonyl chloride of formula D-7 wherein R_4 is 4-cyanophenyl, using the general

procedure for sulfonylation of Example 40 to yield the title compound as a white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR (300 MHz, CD_3OD) δ0.86, 1.23, 1.52–1.67, 1.93, 2.14, 2.56, 3.93, 6.80, 7.05, 7.18, 7.80, 7.86.

EXAMPLES 65–93

Using the general procedure of Example 40, but substituting the appropriate reactants, the following compounds of the present invention are prepared:

EXAMPLE 65

N-[3-[1(R or S)-(6(R or S)-4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

EXAMPLE 66

N-[3-[1(R or S)-(6(S or R)-4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

EXAMPLE 67

N-[3-[1(S or R)-(6(R or S)-4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

EXAMPLE 68

N-[3-[1(S or R)-(6(S or R)-4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

EXAMPLE 69

N-[3-[t-Butyl-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-methyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is t-butyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

EXAMPLE 70

4-Cyano-N-[3-[t-butyl-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-methyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is t-butyl, R_4 is 4-cyanophenyl) Refer to Chart D

EXAMPLE 71

4-Fluoro-N-[3-[t-butyl-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-methyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is t-butyl, R_4 is 4-fluorophenyl) Refer to Chart D

EXAMPLE 72

N-[3-[t-Butyl-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-methyl]-phenyl]-8-quinolinesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is t-butyl, R_4 is quinolin-8-yl) Refer to Chart D

EXAMPLE 73

N-[3-[1-(6-(2-(1-Methyl-1H-imidazole-4-sulfonylamino)-ethyl)-4-hydroxy-2-oxo-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is 2-(1-methylimidazole-4-sulfonylamino)-ethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) Refer to Chart D

EXAMPLE 74

N-[3-[1-(4-Hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-2-pyridinesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 2-pyridyl) Refer to Chart D

EXAMPLE 75

4-Cyano-N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-2-pyridinesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 4-cyano-2-pyridyl) Refer to Chart D

EXAMPLE 76

N-[3-[1-(4-Hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-2-quinolinesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is quinolin-2-yl) Refer to Chart D

EXAMPLE 77

2-Hydroxy-N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 2-hydroxyphenyl) Refer to Chart D

EXAMPLE 78

N-[3-[1-(4-Hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-2-pyrimidinesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 2-pyrimidyl) Refer to Chart D

EXAMPLE 79

N-[3-[1-(4-Hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-2-quinazolinesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is quinazolin-2-yl) Refer to Chart D

EXAMPLE 80

N-[3-[1-(4-Hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-7H-purine-6-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 7H-purin-6-yl) Refer to Chart D

EXAMPLE 81

N-[3-[1-(4-Hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1H-imidazole-2-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 1H-imidazol-2-yl) Refer to Chart D

EXAMPLE 82

N-[3-[1-(4-Hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1H-benzimidazole-2-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 1H-benzimidazol-2-yl) Refer to Chart D

EXAMPLE 83

N-[3-[1-(4-Hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-thiazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is thiazol-2-yl) Refer to Chart D

EXAMPLE 84

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-2-

pyridinesulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 2-pyridyl) Refer to Chart D

EXAMPLE 85

4-Cyano-N-[3-[1-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-2-pyridinesulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 4-cyano-2-pyridyl) Refer to Chart D

EXAMPLE 86

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-2-quinolinesulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is quinolin-2-yl) Refer to Chart D

EXAMPLE 87

2-Hydroxy-N-[3-[1-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 2-hydroxyphenyl) Refer to Chart D

EXAMPLE 88

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-2-pyrimidinesulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 2-pyrimidyl) Refer to Chart D

EXAMPLE 89

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran- 3-yl)-propyl]-phenyl]-2-quinazolinesulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is quinazolin-2-yl) Refer to Chart D

EXAMPLE 90

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-7H-purine-6-sulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 7H-purin-6-yl) Refer to Chart D

EXAMPLE 91

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1H-imidazole-2-sulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 1H-imidazol-2-yl) Refer to Chart D

EXAMPLE 92

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1H-benzimidazole-2-sulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 1H-benzimidazol-2-yl) Refer to Chart D

EXAMPLE 93

N-[3-[1-(4-Hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-thiazole-4-sulfonamide (Formula D-6: R_1 is propyl, R_2 is phenethyl, R_3 is ethyl, R_4 is thiazol-2-yl) Refer to Chart D

EXAMPLE 93A

4-Fluoro-N-[3-[1-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-benzenesulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 4-fluorophenyl) Refer to Chart D

The title compound is prepared from the amine of Preparation 20 (Formula D-5: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) and 4-fluoro benzenesulfonyl chloride using the general procedure for sulfonylation of Example 40 to yield the title compound as an off-white amorphous solid after flash chromatography with 5% EtOAc/CH_2Cl_2.

Physical characteristics are as follows:

^{1}H NMR complicated by presence of diastereomers.

^{1}H NMR (300 MHz, CD_3OD) δ0.75–0.96, 1.31–1.48, 1.57–2.01, 2.09–2.22, 2.48–2.71, 3.92, 3.94, 6.86–7.24, 7.72.

PREPARATION 22

6-(2-Cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2H-pyran-2-one (Formula E-2) Refer to Chart E

To a cold (−78° C.) stirred solution of 1.5 ml of diisopropylamine in 9 ml of dry tetrahydrofuran, under argon, is added 6.2 ml of a 1.6M solution of n-butyllithium in hexane. The solution is warmed to 0° C. and then treated with a solution of 378 mg of commercially available 4-hydroxy-6-methyl-2-pyrone of formula E-1 in 8 ml of hexamethylphosphoramide. After 30 minutes at 0° C., 0.32 ml of bromomethylcyclopropane is added; after another ten minutes, a second portion of the same amount is added. The reaction is stirred, allowed to warm to room temperature overnight, and is then partitioned between ethyl acetate and excess dilute hydrochloric acid. The organic phase is washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is flash chromatographed on silica gel 60 (230–400 mesh) using 25% ethyl acetate in dichloromethane containing 1% acetic acid to provide 371 mg of the title compound, along with 206 mg of monoalkylated material.

Physical characteristics are as follows:

^{1}H NMR δ0.0, 0.4, 0.6, 1.5, 1.6, 2.2, 5.6, 6.1, 7.2–7.3, 11.5;

EI MS m/z=234;

TLC R_f 0.29 (25% ethyl acetate in dichloromethane containing 1% acetic acid).

PREPARATION 23

3-(α-Cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2H-pyran-2-one (Formula E-3) Refer to Chart E

A mixture of 367 mg of the title compound of Preparation 22, 470 mg of the title compound of Preparation F-5, 60 mg of p-toluenesulfonic acid monohydrate, and 1 g of 3 Å molecular sieves in 5 ml of benzene is heated with stirring overnight under argon. The mixture is diluted with dichloromethane and ether and filtered through a pad of sodium sulfate. The solvent is removed under reduced pressure and the residue is flash chromatographed on silica gel 60 (230–400 mesh) using 5–20% ethyl acetate in dichloromethane to afford 399 mg of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ−0.06, 0.3, 0.5, 1.4, 1.5, 2.5, 3.5, 5.1, 7.2–7.4;

EI HRMS m/z=513.2513;

TLC R_f 0.28 (5% ethyl acetate in dichloromethane).

PREPARATION 24

3-(α-Cyclopropyl-meta-aminobenzyl)-6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2H-pyran-2-one (Formula E-4) Refer to Chart E

A mixture of 391 mg of the title compound of Preparation 23 and 100 mg of 5% palladium on carbon in 10 ml of methanol is shaken overnight under 40 psi of hydrogen. The mixture is then filtered through Celite, and the filtrate is concentrated under reduced pressure to provide 280 mg of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.0, 0.2–0.7, 1.4, 1.6, 1.8, 2.6, 6.8, 7.2–7.4;

TLC R_f 0.38 (30% ethyl acetate in dichloromethane.)

EXAMPLE 94

N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-4-fluoro-benzenesulfonamide (Formula E-6) Refer to Chart E

To a mixture of 57 mg of the title compound of Preparation 24 and 24 μL of pyridine in 0.5 mL of dichloromethane is added 29 mg of 4-fluorobenzenesulfonyl chloride. After stirring overnight, the solution is diluted with ethyl acetate and washed with dilute aqueous hydrochloric acid, brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) using 10% ethyl acetate in dichloromethane to give 56 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ–0.07, 0.13, 0.33, 0.54, 1.39, 1.51, 1.72, 2.55, 3.39, 6.12, 6.87, 7.00, 7.08, 7.19, 7.27, 7.72, 9.72;

EI-MS: [M+]=537.1977 found.

EXAMPLES 95–97

Following the procedure described above and using starting materials and reagents known and available to one of ordinary skill in organic synthesis, the following additional compounds are prepared:

EXAMPLE 95

4-Cyano-N-(3-{cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-benzenesulfonamide (Formula E-7) Refer to Chart E

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ–0.03, 0.13, 0.23, 0.36, 0.44, 0.57, 1.41, 1.58, 1.75, 2.57, 3.32, 5.98, 6.89, 7.11, 7.21, 7.68, 7.82;

EI-MS: [M+]=544.2035 found.

EXAMPLE 96

N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-8-quinolinesulfonamide (Formula E-8) Refer to Chart E

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ–0.07, 0.18, 0.37, 0.54, 1.37, 1.51, 2.53, 3.31, 5.96, 6.87, 7.00, 7.13, 7.48, 7.54, 7.92, 8.23, 9.07;

EI-MS: [M+]=570.2188 found.

EXAMPLE 97

N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula E-9) Refer to Chart E

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ–0.08, 0.13, 0.33, 0.56, 1.37, 1.51, 1.73, 2.54, 3.21, 3.60, 5.95, 6.82, 7.0, 7.19, 7.37, 7.5;

EI-MS: [M+]=523.2142 found.

EXAMPLE 98

Chiral HPLC Separation of N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula E-9) to give (R or S)-N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula E-10) and (R or S)-N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula E-11) Refer to Chart E

A stock sample of the title compound of Example 97 (3 mg/ml) in 5.0 mL each of mobile phase (30% isopropanol, 0.1% acetic acid, and 0.2% water in hexane) and isopropanol is prepared. The stock sample is filtered through a 0.45 micron syringe filter and washed with ethanol to give 14.0 mL of clear filtrate. This solution is chromatographed on a 2.0×2.5 cm (R,R) Whelk-O 1 (Regis Technologies, Inc., Morton Grove, Ill. 60053) column at 3.50 mL per injection using an automated chromatographic system. The eluant is monitored and the pools corresponding to the desired peaks from multiple injections are combined, concentrated under reduced pressure and azeotroped with toluene. The residues are dissolved in methanol, filtered through a syringe filter and the filtrates concentrated under reduced pressure to give the title compounds (>95% pure):

(R or S)-N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula E-10)

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ–0.07, 0.14, 0.34, 0.57, 1.32, 1.55, 1.75, 2.51, 3.24, 3.60, 5.87, 6.85, 7.03, 7.15, 7.27, 7.37;

EI-MS: [M+]=523.2149 found.

(R or S)-N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula E-11)

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ–0.07, 0.14, 0.33, 0.55, 1.33, 1.56, 1.75, 2.51, 3.23, 3.60, 5.88, 6.86, 7.03, 7.14, 7.27, 7.38;

EI-MS: [M+]=523.2137 found.

EXAMPLES 99–103

Following the procedure described above and using starting materials and reagents known and available to one of ordinary skill in organic synthesis, the following additional compounds are prepared:

EXAMPLE 99

N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide (Formula E-12)

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ–0.05, 0.07, 0.17, 0.34, 0.55, 1.35, 1.55, 1.7, 2.5, 3.24, 5.86, 6.90, 7.03, 7.15, 7.39, 7.78, 8.60;

EI-MS: [M+]=520;

TLC R_f 0.35 (25% ethyl acetate in dichloromethane).

EXAMPLE 100

N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-2-sulfonamide (Formula E-13)

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ–0.05, 0.15, 0.35, 0.56, 1.35, 1.55, 1.75, 2.53, 3.23, 3.39, 5.89, 6.81, 6.90, 6.97, 7.09, 7.25;

EI-MS: [M+]=523;

TLC R_f 0.31 (5% methanol in dichloromethane).

EXAMPLE 101

N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-benzo-imidazole-2-sulfonamide (Formula E-14)

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ-0.07, 0.1, 0.15, 0.35, 0.56, 1.38, 1.58, 1.65, 2.55, 3.28, 5.95, 6.73, 6.96, 7.10, 7.28, 7.58;

FAB-MS: [M+H]=560.2220 found.

EXAMPLE 102

N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-imidazole-2-sulfonamide (Formula E-15)

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ0.0, 0.25, 0.4, 0.6, 1.4, 1.6, 1.65, 2.6, 3.35, 6.0, 6.8, 7.0, 7.2, 7.4;

EI-MS: [M+]=509;

TLC R_f 0.25 (5% methanol in dichloromethane).

EXAMPLE 103

N-(3-{Cyclopropyl-[6-(2-cyclopropyl-1-cyclopropylmethyl-ethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-quinolinesulfonamide (Formula E-16)

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.0, 0.2, 0.4, 0.6, 1.4, 1.6, 1.7, 2.6, 3.3, 6.0, 7.0–7.2, 7.3, 7.7, 7.8–8.0, 8.2, 8.3;

EI-MS: [M+]=570;

TLC R_f 0.53 (5% methanol in dichloromethane).

PREPARATION 25

Cyclopropyl meta-nitrophenyl ketone (Formula F-2) Refer to Chart F

A 250 ml three necked flask fitted with thermometer and addition funnel is charged with 130 ml of fuming 90% nitric acid and cooled to −10° C. Into the stirred liquid is added dropwise 21 ml of commercially available cyclopropyl phenyl ketone of formula F-1. The rate of addition is regulated to maintain the reaction temperature at about −10° C. Upon completion of addition, the resulting clear yellow solution is stirred for another 10 minutes at −10° C., then poured into 1 L of crushed ice. The precipitated solid is extracted with 700 ml of toluene, and the extract is washed twice with 5% sodium hydroxide solution, once with brine, and dried over magnesium sulfate. The solvent is removed under reduced pressure and the residue is recrystallized from methanol at −25° C. to give 14.6 g of the title compound as dense, pale yellow prisms. The mother liquor contained substantial amounts of the ortho isomer.

Physical characteristics are as follows:

^{1}H NMR δ1.2, 1.3, 2.7, 7.70, 8.3, 8.4, 8.85;

IR 1664, 1529, 1352, 1225, 1082, 1017, 852, 689 cm^{-1};

Anal. Found: C, 62.89; H, 4.73; N, 7.32;

EI MS m/z 191;

TLC R_f 0.32 (25% ethyl acetate in hexane).

PREPARATION 26

meta-Aminophenyl cyclopropyl ketone (Formula F-3) Refer to Chart F

A solution of 5.76 g of the title compound of Preparation 25 is prepared with the aid of heat in 100 ml of methanol. To this is added 450 mg of 5% platinum on carbon catalyst, and the mixture is stirred vigorously under 1 atmosphere of hydrogen. After 5 hours, the mixture is filtered through a pad of Celite and the filtrate concentrated under reduced pressure to afford 4.89 g of the title compound as a greenish oil.

Physical characteristics are as follows:

^{1}H NMR δ1.0, 1.2, 2.6, 3.9, 6.8, 7.2, 7.4;

TLC R_f 0.50 (80% ethyl acetate in hexane).

PREPARATION 27

meta-Benzyloxycarbonylaminophenyl cyclopropyl ketone (Formula F-4) Refer to Chart F

To a cold (0° C.), stirred solution of 4.89 g of the title compound of Preparation 26 and 6.3 ml of diisopropylethylamine in 90 ml of dichloromethane is added dropwise 4.7 ml of benzyl chloroformate. The completed solution is allowed to warm to room temperature. After 4 hours, the mixture is washed with dilute hydrochloric acid, and the aqueous phase extracted with two additional portions of dichloromethane. The combined organic phase is dried over magnesium sulfate and concentrated under reduced pressure to a yellow solid. This is triturated with two 30 ml portions of hexane, these being discarded, and the remaining solid is dried under vacuum to afford 8.74 g of the title compound.

Physical characteristics are as follows:

TLC Rf 0.45 (5% ethyl acetate in dichloromethane).

PREPARATION 28

meta-Benzyloxycarbonylaminophenyl cyclopropyl carbinol (Formula F-5) Refer to Chart F

To a stirred solution of 8.74 g of compound F-4 of Preparation 27 in 100 ml of tetrahydrofuran and 100 ml of ethanol is added, in portions, 4.5 g of sodium borohydride. After 3 hours at room temperature, the mixture is cooled in ice for the addition of 100 ml of 1N hydrochloric acid. The mixture is thrice extracted with dichloromethane, and the combined extract dried over magnesium sulfate. Solvent is removed under reduced pressure and the residue flash chromatographed on silica gel 60 (230–400 mesh) using 40% ethyl acetate in hexane to provide 8.48 g of the title compound as a white crystalline solid. This is optionally recrystallized from ethyl acetate-hexane.

Physical characteristics are as follows:

^{1}H NMR δ0.3–0.6, 1.1, 2.35, 3.92, 5.17, 7.1, 7.2–7.4;

IR 1693, 1599, 1559, 1449, 1235, 1054, 697 cm^{-1};

Anal. Found: C, 72.57; H, 6.51; N, 4.61;

PREPARATION 29

4-Hydroxy-6-[3-(2-methoxy-ethoxy)-propyl]-pyran-2-one (Formula G-1) Refer to Chart G

To a flame-dried flask under an argon atmosphere is added 2.80 mL of diisopropylamine and 20.0 mL of dry tetrahydrofuran. The solution is cooled to −78° C. and treated with 12.5 mL (1.6M in hexane) of n-butyllithium. The solution is warmed to 0° C. for 30 minutes, then treated with 5.0 mL of dry hexamethylphosphoramide. The lithium diisopropylamide solution is then treated with 1.20 g of commercially available 4-hydroxy-6-methyl-2-pyrone of formula G-0 as a solution in 16 mL of dry tetrahydrofuran and 14 mL of dry hexamethylphosphoramide. After 30 minutes the mixture is treated with 2.30 g of 2-(2-methoxy-ethoxy)-ethyl iodide as a solution in 12 mL of dry tetrahydrofuran. The mixture is stirred 1 hour at 0° C. and then warmed to room temperature. After 1 hour the reaction is quenched with excess 1N aqueous hydrochloric acid. The mixture is concentrated under reduced pressure and partioned between dichloromethane and water. The aqueous phase is extracted with sufficient volumes of dichloromethane to remove the title compound. The combined organic extracts are washed with brine, dried over magnesium sulfate and concentrated under

reduced pressure. The residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 30% ethyl acetate in dichloromethane containing 3% acetic acid to 80% ethyl acetate in dichloromethane containing 5% acetic acid to give 1.34 g of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ1.93, 2.54, 3.39, 3.55, 5.55, 5.90;

TLC R_f 0.26 (50% ethyl acetate in dichloromethane containing 5% acetic acid).

PREPARATION 30

3-(α-Cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-4-hydroxy-6-[3-(2-methoxy-ethoxy)-propyl]-pyran-2-one (Formula G-2) Refer to Chart G

A mixture of 146 mg of the title compound of Preparation 29, 340 mg of the title compound of Preparation 28, prepared as described in Chart F, 25 mg of p-toluenesulfonic acid monohydrate, and 0.5 g of 3 Å molecular sieves in 5 mL of dichloromethane is heated overnight with stirring. The mixture is cooled and the solvent removed under reduced pressure. The residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 5% to 10% methanol in ethyl acetate to give 129 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.25, 0.45, 0.67, 1.77, 2.39, 3.38, 3.51, 5.13, 5.84, 7.17, 7.32, 7.42;

EI-MS: [M+]=507.2257 found;

TLC R_f 0.28 (50% ethyl acetate in dichloromethane).

PREPARATION 31

3-(α-Cyclopropyl-meta-aminobenzyl)-4-hydroxy-6-[3-(2-methoxy-ethoxy)-propyl]-pyran-2-one (Formula G-3) Refer to Chart G

A mixture of 124 mg of the title compound of Preparation 30 and 35 mg of 5% palladium on charcoal in 5 mL of ethanol is shaken overnight under 50 psi of hydrogen. The mixture is filtered through Celite with ethanol washes of the filter cake. The filtrates are combined and the solvent removed under reduced pressure to give 92 mg of the title compound. Physical characteristics are as follows:

TLC R_f 0.12 (ethyl acetate).

EXAMPLE 104

N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{2-methoxy-ethoxy}-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula G-4) Refer to Chart G

To a mixture of 37 mg of the title compound of Preparation 31 and 18 μL of pyridine in 0.5 mL of dichloromethane is added 20 mg of 1-methylimidazole-4-sulfonyl chloride. After stirring overnight, the solvent is removed under reduced pressure. The residue is azeotroped with toluene and is then purified by flash column chromatography on silica gel 60 (230–400 mesh) using 2% to 8% methanol in dichloromethane to give 32 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.1, 0.24, 0.45, 0.65, 1.75, 1.85, 2.46, 3.30, 3.34, 3.50, 5.98, 6.98, 7.08, 7.19, 7.29, 7.42;

EI-MS: [M+]=517.1874 found;

TLC R_f 0.22 (5% methanol in dichloromethane).

PREPARATION 32

3-(α-Cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-4-hydroxy-6-methyl-pyran-2-one (Formula H-1) Refer to Chart H

A mixture of 493 mg of commercially available 4-hydroxy-6-methyl-2-pyrone of formula H-0, 592 mg of the title compound of Preparation 28, prepared as described in Chart F and 56 mg of p-toluenesulfonic acid monohydrate in 20 mL of dichloromethane is heated to reflux through an addition funnel containing 3 Å molecular sieves for 6 hours. The mixture is cooled and the solvent removed under reduced pressure. The residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 60% to 100% ethyl acetate in dichloromethane to give 470 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.23, 0.43, 0.66, 1.78, 3.41, 5.09, 5.89, 7.00, 7.14, 7.29, 7.37, 10.1;

EI-MS: [M+]=405;

TLC R_f 0.52 (ethyl acetate).

PREPARATION 33

3-(α-Cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-4-hydroxy-6-propyl-pyran-2-one (Formula H-2) Refer to Chart H

To a flame-dried flask under an argon atmosphere is added 0.45 mL of diisopropylamine and 3.0 mL of dry tetrahydrofuran. The solution is cooled to −78° C. and treated with 2.0 mL (1.6M in hexane) of n-butyllithium. The solution is warmed to 0° C. for 15 minutes, then cooled to −78° C. The lithium diisopropylamide solution is treated with 405 mg of the title compound of Preparation 32 as a solution in 4 mL of dry tetrahydrofuran. After 1 hour at −78° C. the mixture is treated with 85 μL of ethyl bromide. The mixture is then stirred at −78° C. for 3 hours. The reaction is quenched with excess 1N aqueous hydrochloric acid. The mixture is warmed and partioned between ethyl acetate and phosphate buffer. The aqueous phase is extracted twice with ethyl acetate. The combined organic extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 10% to 20% ethyl acetate in dichloromethane to give 277 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.24, 0.45, 0.65, 0.88, 1.55, 1.79, 2.28, 3.42, 5.10, 5.95, 6.89, 7.15, 7.3, 10.0;

EI-MS: [M+]=433;

TLC R_f 0.33 (10% ethyl acetate in dichloromethane).

PREPARATION 34

3-(α-Cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-6-[1-ethyl-3-(2-methoxy-ethoxy)-propyl]-4-hydroxy-pyran-2-one (Formula H-3) Refer to Chart H

To a flame-dried flask under an argon atmosphere is added 0.30 mL of diisopropylamine and 2.0 mL of dry tetrahydrofuran. The solution is cooled to −78° C. and treated with 1.3 mL (1.6M in hexane) of n-butyllithium. The solution is warmed to 0° C. for 15 minutes, then cooled to −78° C. The lithium diisopropylamide solution is treated with 277 mg of the title compound of Preparation 33 as a solution in 3 mL of dry tetrahydrofuran. After 1 hour at −78° C., the mixture is treated with 180 mg of 2-(2-methoxy-ethoxy)-ethyl iodide in 3 mL of tetrahydrofuran. The mixture is then stirred at −78° C. for 3 hours. The reaction is quenched with excess 1N aqueous hydrochloric acid. The mixture is warmed and partioned between ethyl acetate and phosphate buffer. The aqueous phase is extracted thrice with ethyl acetate. The combined organic extracts are washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 25% to 40% ethyl acetate in dichloromethane to give 198 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.25, 0.46, 0.66, 0.75, 1.5, 1.76, 2.36, 3.4, 5.15, 5.96, 7.2, 7.3, 7.42, 10.0;

EI-MS: [M+]=535;

TLC R_f 0.29 (25% ethyl acetate in dichloromethane).

PREPARATION 35

3-(α-Cyclopropyl-meta-aminobenzyl)-6-[1-ethyl-3-(2-methoxy-ethoxy)-propyl]-4-hydroxy-pyran-2-one (Formula H-4) Refer to Chart H

A mixture of 180 mg of the title compound of Preparation 34 and 50 mg of 5% palladium on charcoal in 2 mL of ethanol is shaken overnight under 50 psi of hydrogen. The mixture is filtered through Celite with ethanol washes of the filter cake. The filtrates are combined and the solvent removed under reduced pressure to give 127 mg of the title compound.

Physical characteristics are as follows:

TLC R_f 0.19 (ethyl acetate).

EXAMPLE 105

N-(3-{Cyclopropyl-[6-(1-ethyl-3-{2-methoxy-ethoxy}-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula H-5) Refer to Chart H

To a mixture of 32 mg of the title compound of Preparation 35 and 13 μL of pyridine in 0.8 mL of dichloromethane is added 14.5 mg of 1-methylimidazole-4-sulfonyl chloride. After stirring overnight, the solvent is removed under reduced pressure. The residue is azeotroped with toluene and is then purified by flash column chromatography on silica gel 60 (230–400 mesh) using 1% to 4% methanol in dichloromethane to give 38 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.05, 0.25, 0.45, 0.65, 0.83, 1.5–2.0, 2.45, 3.3–3.5, 3.62, 6.00, 6.99, 7.1–7.3, 7.48;

EI-MS: [M+]=545.2186 found;

TLC R_f 0.24 (5% methanol in dichloromethane).

EXAMPLE 106

4-Cyano-N-(3-{cyclopropyl-[6-(1-ethyl-3-{2-methoxy-ethoxy}-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-benzenesulfonamide

Following the procedure described above and using starting materials and reagents known and available to one of ordinary skill in organic synthesis, the title compound is prepared.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.15, 0.25, 0.45, 0.65, 0.78, 1.2–1.8, 2.4, 3.3–3.6, 3.54, 5.89, 6.95, 7.1–7.3, 7.6–7.9;

FAB-MS: [M+H]=567.2176 found;

TLC R_f 0.40 (50% ethyl acetate in dichloromethane).

PREPARATION 36

3-(α-Cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-6-(1-ethyl-3-hydroxy-propyl)-4-hydroxy-pyran-2-one (Formula I-1) Refer to Chart I

To a flame-dried flask under an argon atmosphere is added 0.46 mL of diisopropylamine and 3.5 mL of dry tetrahydrofuran. The solution is cooled to −78° C. and treated with 2.0 mL (1.6M in hexane) of n-butyllithium. The solution is warmed to 0° C. for 20 minutes, then cooled to −78° C. The lithium diisopropylamide solution is treated with 433 mg of the title compound of Preparation 33 as a solution in 4 mL of dry tetrahydrofuran. After 1 hour at −78° C. the mixture is treated with gaseous ethylene oxide for 5 minutes. The mixture is then stirred at −78° C. for 15 minutes. The reaction is quenched with excess 1N aqueous hydrochloric acid. The mixture is warmed and partioned between dichloromethane and phosphate buffer. The aqueous phase is extracted twice with dichloromethane. The combined organic extracts are washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 2% to 8% methanol in dichloromethane to give 144 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.22, 0.45, 0.65, 0.7, 1.3–1.7, 1.8, 2.25, 3.4, 5.1, 5.91, 7.1–7.4;

FAB-MS: [M+H]=478;

TLC R_f 0.29 (5% methanol in dichloromethane).

PREPARATION 37

6-(3-Bromo-1-ethyl-propyl)-3-(α-cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-4-hydroxy-pyran-2-one (Formula I-2) Refer to Chart I

To a stirring solution of 114 mg of the title compound of Preparation 36 in 3 mL of tetrahydrofuran is added 160 mg of triphenylphosphine and 200 mg of carbon tetrabromide. After 2 hours, the solvent is removed under reduced pressure and the residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 70% to 100% diethyl ether in hexane to give 113 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.25, 0.35, 0.55, 0.65, 0.84, 1.5–2.2, 3.2, 3.35, 3.52, 5.16, 5.95, 6.79, 7.1–7.4;

FAB-MS: [M+H]=504.1404 found;

TLC R_f 0.29 (75% diethyl ether in hexane).

PREPARATION 38

6-(3-Azido-1-ethyl-propyl)-3-(α-cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-4-hydroxy-pyran-2-one (Formula I-3) Refer to Chart I

To a stirring solution of 113 mg of the title compound of Preparation 37 in 2.0 mL of ethanol is added 55 mg of sodium azide and 0.5 mL of water. The reaction mixture is heated overnight and then cooled. The solvent is removed under reduced pressure and the residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with diethyl ether to give 89 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.23, 0.33, 0.51, 0.68, 0.82, 1.4–2.0, 2.33, 3.1–3.3, 3.5, 5.15, 5.94, 6.84, 7.1–7.4;

EI-MS: [M+]=502;

TLC R_f 0.52 (10% ethyl acetate in dichloromethane).

PREPARATION 39

6-(3-Amino-1-ethyl-propyl)-3-(α-cyclopropyl-meta-aminobenzyl)- 4-hydroxy-pyran-2-one (Formula I-4) Refer to Chart I

A mixture of 87 mg of the title compound of Preparation 38 and 35 mg of 5% palladium on charcoal in 4 mL of ethanol is shaken for 4 hours under 40 psi of hydrogen. The mixture is filtered through Celite with ethanol washes of the filter cake. The filtrates are combined and the solvent removed under reduced pressure to give 70 mg of the title compound as a mixture with 6-(3-amino-1-ethyl-propyl)-3-(α-cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-4-hydroxy-pyran-2-one.

Physical characteristics are as follows:

TLC R_f 0.05 (5% methanol in dichloromethane).

PREPARATION 40

3-(Cyclopropyl-{3-[1-methyl-1H-imidazole-4-sulfonylamino]-phenyl}-methyl)-6-({1-ethyl-3-[1-methyl-

1H-imidazole-4-sulfonylamino]}-propyl)-2-oxo-2H-pyran-4-yl 1-methyl-1H-imidazole-4-sulfonate (Formula I-5) Refer to Chart I

To a mixture of 70 mg of the title compound of Preparation 39 and 6-(3-amino-1-ethyl-propyl)-3-(α-cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-4-hydroxy-pyran-2-one, also from Preparation 39, in 1.5 mL of dichloromethane is added 120 μL of diisopropylethylamine and 92 mg of 1-methylimidazole-4-sulfonyl chloride. After stirring overnight, the solvent is removed under reduced pressure. The residue is azeotroped with toluene and is then purified by flash column chromatography on silica gel 60 (230–400 mesh) using 2% to 6% methanol in dichloromethane to give 49 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.2–0.5, 0.75, 0.90, 1.4–2.0, 2.55, 3.0–3.4, 3.6–3.7, 6.63, 7.0–7.7;

TLC R_f 0.14 (5% methanol in dichloromethane).

EXAMPLE 107

N-(3-{Cyclopropyl-[6-(1-ethyl-3-{1-methyl-1H-imidazole-4-sulfonylamino}-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula I-6) Refer to Chart I

A solution of 49 mg of the title compound of Preparation 40 in 4 mL methanol containing ammonia is cooled to 0° C. and treated with gaseous ammonia. After 5 minutes ammonia introduction is ceased, the flask is tightly capped and warmed to room temperature. After standing overnight the solvent is removed under reduced pressure and the residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 3% to 9% methanol in dichloromethane to give 32 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.2–0.5, 0.75, 0.90, 1.4–2.0, 2.55, 3.0–3.4, 3.6–3.7, 6.63, 7.0–7.7;

EI-MS: [M+]=523;

TLC R_f 0.33 (5% methanol in dichloromethane).

PREPARATION 41

3-(α-Cyclopropyl-meta-aminobenzyl)-6-(1-ethyl-3-hydroxypropyl)-4-hydroxy-pyran-2-one (Formula J-1) Refer to Chart J

A mixture of 477 mg of the title compound of Preparation 36 and 150 mg of 5% palladium on charcoal in 10 mL of ethanol is shaken overnight under 45 psi of hydrogen. The mixture is filtered through Celite with ethanol washes of the filter cake. The filtrates are combined and the solvent is removed under reduced pressure to give 340 mg of the title compound.

Physical characteristics are as follows:

TLC R_f 0.10 (5% methanol in dichloromethane).

PREPARATION 42

6-(3-Bromo-1-ethyl-propyl)-3-(α-cyclopropyl-meta-aminobenzyl)-4-hydroxy-pyran-2-one (Formula J-2) Refer to Chart J

To a stirring solution of 340 mg of the title compound of Preparation 41 in 7 mL of tetrahydrofuran is added 525 mg of triphenylphosphine and 663 mg of carbon tetrabromide. After 30 minutes, the solvent is removed under reduced pressure and the residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 30% to 50% ethyl acetate in dichloromethane to give 228 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$) δ0.19, 0.42, 0.58, 0.75, 1.4–2.4, 3.14, 3.3, 5.26, 6.15, 6.47, 6.91, 7.00;

TLC R_f 0.45 (5% methanol in dichloromethane).

EXAMPLE 108

N-(3-{[6-(3-Bromo-1-ethyl-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-cyclopropyl-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula J-3) Refer to Chart J

To a mixture of 102 mg of the title compound of Preparation 42 and 40 μL of pyridine in 1.0 mL of dichloromethane is added 45 mg of 1-methylimidazole-4-sulfonyl chloride. After stirring overnight, the solvent is removed under reduced pressure. The residue is azeotroped with toluene and is then purified by flash column chromatography on silica gel 60 (230–400 mesh) using 2% to 5% methanol in dichloromethane to give 86 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ0.2, 0.44, 0.60, 0.82, 1.4–2.2, 2.5, 3.1–3.4, 3.62, 5.93, 6.92, 7.07, 7.19, 7.30, 7.40;

FAB-MS: [M+H]=550.1037 found;

TLC R_f 0.36 (5% methanol in dichloromethane).

EXAMPLE 109

N-(3-}[6-(3-Azido-1-ethyl-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-cyclopropyl-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula J-4) Refer to Chart J

To a stirring solution of 113 mg of the title compound of Example 108 in 1.2 mL of ethanol is added 50 mg of sodium azide and 0.4 mL of water. The reaction mixture is heated overnight and then cooled. The solvent is removed under reduced pressure and the residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 3% to 6% methanol in dichloromethane to give 57 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ0.25, 0.48, 0.66, 0.90, 1.3–1.8, 2.42, 2.9–3.2, 3.68, 5.94, 6.93, 7.12, 7.19, 7.23, 7.35, 7.46;

FAB-MS: [M+H]=550.1037 found;

TLC R_f 0.36 (5% methanol in dichloromethane).

PREPARATION 43

N-(3-{[6-(3-Amino-1-ethyl-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-cyclopropyl-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula J-5) Refer to Chart J

A mixture of 104 mg of the title compound of Example 109 and 30 mg of 5% palladium on charcoal in 2 mL of each of methanol and ethanol is shaken overnight under 45 psi of hydrogen. The mixture is filtered through Celite with methanol washes of the filter cake. The filtrates are combined and the solvent is removed under reduced pressure to give 69 mg of the title compound.

Physical characteristics are as follows:

TLC R_f 0.05 (5% methanol in dichloromethane).

EXAMPLE 110

2-[[8-[[3-[3-[Cyclopropyl[3-[[(1-methyl-1H-imidazol-4-yl)sulfonyl]amino]phenyl]methyl]-4-hydroxy-2-oxo-2H-pyran-6-yl]pentyl]amino]-1,8-dioxooctyl]methylamino]-ethane sulfonic acid, monosodium salt (Formula J-6) Refer to Chart J

A suspension of 69 mg of the title compound of Preparation 43 in 1.0 mL of dichloromethane is treated with 0.22 mL (0.65M in acetonitrile) of the triethylamine salt of suleptanic acid and 25 μL of diisopropylcarbodiimide. After 1 hour the mixture is treated with 0.5 mL of dimethylformamide. After stirring overnight the solvent is removed under reduced pressure and the residue is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 10% to 30% methanol in dichloromethane. The crude product is dissolved in water saturated n-butanol and partioned with saturated aqueous sodium sulfate. The aqueous phase is extracted twice with additional portions of water saturated n-butanol. The combined n-butanol layers are filtered through a pad of sodium sulfate and concentrated under reduced pressure to give 94 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR ($CDCl_3$—CD_3OD) δ0.05–0.6, 0.83, 1.1–2.5, 2.9–3.7, 3.68, 5.84, 6.8–7.6;

FAB-MS: [M+H]=786.2838 found;

TLC R_f 0.21 (20% methanol in dichloromethane).

EXAMPLES 111–134

Utilizing procedures described above and using starting materials and reagents known and available to one of ordinary skill in organic synthesis, the following additional compounds are prepared:

111) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[(2-hydroxy-1,1-bis{hydroxymethyl}-ethyl)-amino]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-benzenesulfonamide

112) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[(2-hydroxy-1,1-bis{hydroxymethyl}-ethyl)-amino]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide

113) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[(2-hydroxy-1,1-bis{hydroxymethyl}-ethyl)-amino]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-imidazole-2-sulfonamide

114) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[(2-hydroxy-1,1-bis{hydroxymethyl}-ethyl)-amino]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-benzoimidazole-2-sulfonamide

115) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[(2-hydroxy-1,1-bis{hydroxymethyl}-ethyl)-amino]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide

116) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[(2-hydroxy-1,1-bis{hydroxymethyl}-ethyl)-amino]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-2-sulfonamide

117) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{γ-L-glutamyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-benzenesulfonamide

118) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{γ-L-glutamyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide

119) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{γ-L-glutamyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-imidazole-sulfonamide

120) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{γ-L-glutamyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-benzoimidazole-sulfonamide

121) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{γ-L-glutamyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide

122) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{γ-L-glutamyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-2-sulfonamide

123) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[piperazin-1-yl]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-benzenesulfonamide

124) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[piperazin-1-yl]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide

125) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[piperazin-1-yl]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-imidazole-2-sulfonamide

126) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[piperazin-1-yl]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-benzoimidazole-2-sulfonamide

127) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[piperazin-1-yl]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide

128) N-(3-{Cyclopropyl-[4-hydroxy-6-(3-{[piperazin-1-yl]-carbonyl}-amino-propyl)-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-2-sulfonamide

129) 2-[[8-[[3-[3-[Cyclopropyl[3-[[phenylsulfonyl]amino]phenyl]methyl]-4-hydroxy-2-oxo-2H-pyran-6-yl]propyl]amino]-1,8-dioxooctyl]methylamino]-ethanesulfonic acid, monosodium salt

130) 2-[[8-[[3-[3-[Cyclopropyl[3-[[(2-pyridyl)sulfonyl]amino]phenyl]methyl]-4-hydroxy-2-oxo-2H-pyran-6-yl]propyl]amino]-1,8-dioxooctyl]methylamino]-ethane sulfonic acid, monosodium salt

131) 2-[[8-[[3-[3-[Cyclopropyl[3-[[(1H-benzimidazol-2-yl)sulfonyl]amino]phenyl]methyl]-4-hydroxy-2-oxo-2H-pyran-6-yl]propyl]amino]-1,8-dioxooctyl]methyl amino]-ethanesulfonic acid, monosodium salt

132) 2-[[8-[[3-[3-[Cyclopropyl[3-[[(1H-imidazol-2-yl) sulfonyl]amino]phenyl]methyl]-4-hydroxy-2-oxo-2H-pyran-6-yl]propyl]amino]-1,8-dioxooctyl] methylamino]-ethane sulfonic acid, monosodium salt

133) 2-[[8-[[3-[3-[Cyclopropyl[3-[[(1-methyl-1H-imidazol-4-yl)sulfonyl]amino]phenyl]methyl]-4-hydroxy-2-oxo-2H-pyran-6-yl]propyl]amino]-1,8-dioxooctyl]methylamino]-ethanesulfonic acid, monosodium salt

134) 2-[[8-[[3-[3-[Cyclopropyl[3-[[(1-methyl-1H-imidazol-2-yl)sulfonyl]amino]phenyl]methyl]-4-hydroxy-2-oxo-2H-pyran-6-yl]propyl]amino]-1,8-dioxooctyl]methylamino]-ethane sulfonic acid, monosodium salt

PREPARATION 44

(Tetrahydropyran-4-yl)-methanol (Formula K-2) Refer to Chart K

To a cold (0°), stirred solution of 651 mg of tetrahydropyran-4-carboxylic acid in 2.5 ml of dry tetrahydrofuran, under argon, is added dropwise 10 ml of a 1.0M solution of borane in tetrahydrofuran. After 18 hours at room temperature, the solution is recooled to 0° and quenched with 1 ml of 1M KOH. The mixture is acidified with 1M aqueous hydrochloric acid and extracted four times with dichloromethane. The extract is dried over magnesium sulfate and concentrated carefully under reduced pressure to afford 0.72 g of the alcohol as a colorless liquid.

Physical characteristics are as follows:

^{1}H NMR δ1.2–1.4, 1.6, 1.8, 3.3–3.4, 3.6, 4.0 ppm.

PREPARATION 45

(Tetrahydropyran-4-yl)-methyl p-toluenesulfonate (Formula K-3) Refer to Chart K

To a cold (0°), stirred solution of 5 mmol of the title compound of Preparation 44 and 0.81 ml of pyridine in 5 ml of dichloromethane is added 1.05 g of p-toluenesulfonyl chloride, and the solution is allowed to warm to room temperature. After 18 hours the mixture is partitioned between ethyl acetate and dilute aqueous hydrochloric acid, and the organic phase is washed with brine and dried over magnesium sulfate. Following removal of solvent under reduced pressure, the residue is flash chromatographed on

silica using 50% ethyl acetate in hexane to afford 1.23 g of the title compound as a colorless liquid.

Physical characteristics are as follows:

^{1}H NMR δ1.2–1.4, 1.6, 1.9–2.0, 2.46, 3.34, 3.85, 3.95, 7.3, 7.8 ppm.

MS: 270

PREPARATION 46

(Tetrahydropyran-4-yl)-methyl iodide (Formula K-4) Refer to Chart K

A solution of 800 mg of tosylate of Preparation 45 and 887 mg of sodium iodide in 6 ml of acetone is refluxed under nitrogen for six hours, then partitioned between ether and dilute aqueous sodium thiosulfate. The organic phase is washed with brine, dried over magnesium sulfate, and concentrated carefully under atmospheric pressure to give 648 mg of the iodide as a colorless liquid.

Physical characteristics are as follows:

^{1}H NMR δ1.2–1.4, 1.6–1.9, 3.1, 3.37, 3.97 ppm.

PREPARATION 47

6-(1-(Tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxypyran-2-one (Formula K-5) Refer to Chart K

To a cold (−78°) stirred solution of 0.90 ml of diisopropylamine in 5 ml of tetrahydrofuran, under argon, is added via syringe 3.7 ml of a 1.6M solution of n-butyllithium in hexane. The solution is warmed to 0°, and after ten minutes, a solution of 431 mg of the title compound of Preparation 50 in 3 ml of hexamethylphosphoramide is added via cannula. After 20 minutes, the deep red solution is cooled to −50°, and 605 mg of iodide of Preparation 46 in 1 ml of tetrahydrofuran is added via cannula. The reaction is allowed to warm slowly to 0° and then quenched by addition of pH 7 phosphate buffer. Following removal of tetrahydrofuran under reduced pressure, the residual liquid is acidified with dilute aqueous hydrochloric acid and the resulting precipitate extracted with two portions of ethyl acetate. The organic is washed with dilute aqueous hydrochloric acid and brine, dried over magnesium sulfate, and concentrated under reduced pressure. Flash chromatography of the residue on silica using 5% acetic acid and 30–40% ethyl acetate in dichloromethane provides 553 mg of the title compound as a thick yellow gum.

Physical characteristics are as follows:

TLC R_f 0.36 (5% acetic acid, 65% ethyl acetate in dichloromethane)

^{1}H NMR δ0.85, 1.2–1.8, 2.45, 3.34, 3.9, 5.56, 5.94 ppm.

MS: 252

PREPARATION 48

3-[(3-Benzyloxycarbonylaminophenyl)-cyclopropylmethyl]-6-(1-(tetrahydropyran-4-ylmethyl)-propyl-4-hydroxypyran-2-one (Formula K-6) Refer to Chart K

A solution of 549 mg of alkylation product of Preparation 47, 970 mg of 3-benzyloxycarbonylaminophenyl cyclopropyl carbinol, and 60 mg of p-toluenesulfonic acid monohydrate in 5 ml of dichloromethane is refluxed through 10 ml of 3 Å sieves for 18 hours. Following removal of solvent under reduced pressure, the residue is flash chromatographed on silica using 25–100% ethyl acetate in dichloromethane to 5% methanol in ethyl acetate, providing 511 mg of the title compound as a tan solid.

Physical characteristics are as follows:

TLC R_f 0.32 (30% ethyl acetate in dichloromethane)

^{1}H NMR δ0.2, 0.5, 0.7, 0.8, 1.3–1.7, 3.27, 3.42, 3.86, 5.13, 5.96, 7.1–7.4 ppm.

MS: 531

PREPARATION 49

3-[(3-Aminophenyl)-cyclopropylmethyl]-6-(1-(tetrahydropyran-4-ylmethyl)-propyl-4-hydroxy-pyran-2-one (Formula K-7) Refer to Chart K

A mixture of 510 mg of the title compound of Preparation 48, 605 mg of ammonium formate, and 100 mg of 5% palladium on carbon in 8 ml of methanol is stirred under argon for three hours, then filtered through diatomaceous earth. The filtrate is concentrated under reduced pressure, and the residue flash chromatographed on silica using 2–4% methanol in dichloromethane to afford 280 mg of the title amine as a white solid.

Physical characteristics are as follows:

TLC R_f 0.33 (5% methanol in dichloromethane)

^{1}H NMR δ0.24, 0.42, 0.53, 0.68, 0.84, 1.1–1.7, 2.35, 3.33, 3.6, 3.9, 5.82, 6.5, 6.83, 6.9, 7.11 ppm.

EXAMPLE 135

N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula K-8) Refer to Chart K

To a stirred solution of 60 mg of the amine of Preparation 49 and 24 μL of pyridine in 0.5 ml of dichloromethane is added 27 mg of 1-methylimidazole-4-sulfonyl chloride. After 18 hours the reaction is flashed on silica using 3–6% methanol in dichloromethane to afford 70 mg of the title compound as a white solid.

Physical characteristics are as follows:

TLC R_f 0.24 (5% methanol in dichloromethane)

^{1}H NMR δ0.12, 0.26, 0.45, 0.60, 0.82, 1.1–1.9, 2.3, 3.3, 3.58, 3.9, 6.00, 6.9–7.5 ppm.

HRMS: 541.2238

PREPARATION 50

4-Hydroxy-6-propylpyran-2-one (Formula K-9) Refer to Chart K

To a cold (−78°), stirred solution of 6.3 ml of diisopropylamine in 40 ml of dry tetrahydrofuran, under argon, is added 27.5 ml of a 1.6M solution of butyllithium in hexane. The solution is brought to 0°, and into this is cannulated a solution of 2.52 g of 4-hydroxy-6-methyl-2-pyrone of formula K-10 in 20 ml of hexamethylphosphoric triamide. The deep red solution is stirred 30 minutes at 0°, then cooled to −45° for the addition of 1.5 ml of ethyl bromide. The solution is warmed to 0° and quenched with 60 ml of 1N aqueous hydrochloric acid. Tetrahydrofuran is removed under reduced pressure and the residue extracted five times with ethyl acetate. The organic phase is washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel using 4% acetic acid and 16% ethyl acetate in dichloromethane provides 2.34 g of the title compound as a waxy yellow solid.

Physical characteristics are as follows:

TLC R_f 0.29 (5% acetic acid and 15% ethyl acetate in dichloromethane)

^{1}H NMR δ0.98, 1.6, 2.4, 5.63, 6.05

PREPARATION 51

4-Hydroxy-6-phenethyl-2H-pyran-2-one (Formula L-2) Refer to Chart L

To a flame-dried flask containing a stirred solution of 0.90 mL of diisopropylamine in 6 mL of anhydrous tetrahydrofuran at −78° C. under an argon atmosphere is added 4.0 mL of a 1.6M solution of n-butyllithium in hexane. The resulting solution is allowed to warm to 0° C. for 20 min, and is then treated via cannula with a solution of 378 mg of commercially available 4-hydroxy-6-methyl-2-pyrone of formula L-1 in 15 mL of tetrahydrofuran. The resulting red, thick slurry is slowly treated with 6.0 mL of distilled hexamethylphosphoramide and allowed to stir for 30 min. The red,

cloudy solution is then treated with 0.36 mL of benzyl bromide. The reaction quickly becomes a deep orange solution and is allowed to stir at 0° C. for an additional 60 min. The mixture is quenched with excess 1N aqueous hydrochloric acid and the resulting yellow, biphasic mixture is concentrated to remove the tetrahydrofuran. The resulting mixture is partitioned between dichloromethane and water and the acidic aqueous phase is further extracted with additional portions of dichloromethane. The combined organic phase is dried over magnesium sulfate and then concentrated under reduced pressure. The resulting material is diluted with a large volume of diethyl ether and washed with dilute aqueous hydrochloric acid. The ethereal phase is washed with two additional portions of aqueous hydrochloric acid, once with brine, dried over magnesium sulfate, and finally concentrated under reduced pressure. The residue is flash column chromatographed on silica gel 60 (230–400 mesh) eluting with 1% acetic acid and 20% to 40% ethyl acetate in dichloromethane to give 440 mg of the title compound as a tan solid.

Physical characteristics are as follows:

^{1}H NMR δ2.7, 3.0, 5.46, 5.84, 7.1–7.3.

TLC R_f 0.38 (1% acetic acid and 25% ethyl acetate in dichloromethane.)

MP 137°–138° C.

PREPARATION 52

6-(α-Ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one (Formula L-3) Refer to Chart L

To a cold (−78° C.) stirred solution of 0.29 ml of diisopropylamine in 4 ml of dry tetrahydrofuran, under argon, is added 1.2 ml of a 1.6M solution of n-butyllithium in hexane. The solution is warmed to 0° C., kept at that temperature for ten minutes, then cooled to −30° C. Into this solution is cannulated a solution of 189 mg of the title compound of Preparation 51 in 4 ml of tetrahydrofuran. The resulting heterogeneous mixture is warmed to 0°, and sufficient hexamethylphosphoramide (ca 1 ml) is added to render the mixture mostly homogeneous. After the mixture is stirred for 30 minutes at 0° C., 77 μL of ethyl iodide is added dropwise. After another 90 minutes, the reaction is quenched with excess 1N aqueous hydrochloric acid, and tetrahydrofuran is removed under reduced pressure. The residue is extracted with three portions of ethyl acetate, and the combined organic extract washed with dilute aqueous hydrochloric acid, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is flash chromatographed on silica gel 60 (230–400 mesh) using 1% acetic acid and 25% ethyl acetate in dichloromethane to provide 182 mg of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.85, 1.6, 2.6, 2.9, 5.59, 5.86, 7.0–7.3.

FAB MS [m+H]=245.1185.

TLC R_f 0.33 (1% acetic acid and 25% ethyl acetate in dichloromethane.)

PREPARATION 53

3-(α-Cyclopropyl-meta-(benzyloxycarbonylamino)benzyl)-6-(α-ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one (Formula L-4) Refer to Chart L

A mixture of 181 mg of the title compound of Preparation 52, 220 mg of the compound of formula F-5, 28 mg of p-toluenesulfonic acid monohydrate, and 600 mg of 3 Å molecular sieves in 2 ml of benzene is refluxed under argon for 21 hours, then cooled and filtered through Celite. The filtrate is concentrated under reduced pressure, and the residue flash chromatographed on silica gel 60 (230–400 mesh) using 50–100% ethyl acetate in hexane to provide 250 mg of a mixture of materials. This is re-subjected to silica gel chromatography, using 5–20% ethyl acetate in dichloromethane, to afford 154 mg (40%) of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.26, 0.48, 0.67, 0.81, 1.6, 1.8, 2.5, 2.7, 2.9, 3.48, 5.14, 5.86, 6.81, 7.0–7.5, 9.46.

EI HRMS m/z=523.2350.

TLC R_f 0.27 (5% ethyl acetate in dichloromethane.)

PREPARATION 54

3-(α-Cyclopropyl-meta-aminobenzyl)-6-(α-ethyl-phenethyl)-4-hydroxy-2H-pyran-2-one (Formula L-5) Refer to Chart L

A mixture of 146 mg of the title compound of Preparation 53 and 50 mg of 5% palladium on carbon in 2 ml of methanol is shaken under 40 psi of hydrogen for two hours, then filtered through Celite. The filtrate is concentrated under reduced pressure to give 105 mg (96%) of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.25, 0.5, 0.65, 0.81, 1.6, 2.5, 2.7, 2.9, 3.4, 5.79, 6.5, 6.8–7.3.

TLC R_f 0.38 (30% ethyl acetate in dichloromethane).

EXAMPLES 136–150

Utilizing procedures analogous to those described above, and reacting the compound of formula L-5 with the appropriate sulfonyl chloride, the following additional compounds of the present invention are prepared. Individual stereoisomers are prepared by chiral HPLC resolution of intermediates such as the compounds of formulas L-3, L-4, L-5 and L-6. (Refer to Chart L).

136) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.29 (5% methanol in dichloromethane)

^{1}H NMR δ0.2, 0.5, 0.65, 0.86, 1.63, 1.80, 2.51, 2.8, 3.3, 3.62, 5.7, 6.8–7.4 ppm.

HRMS: 533.1998

137) N-(3-(R or S)-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.32 (5% methanol in dichloromethane)

^{1}H NMR δ0.18, 0.43, 0.63, 0.83, 1.6, 1.75, 2.5, 2.7–2.9, 3.3, 3.55, 5.76, 6.9–7.4 ppm.

HRMS: 533.1983

138) N-(3-(R or S)-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo- 2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.30 (5% methanol in dichloromethane)

^{1}H NMR δ0.2, 0.5, 0.65, 0.86, 1.63, 1.80, 2.51, 2.8, 3.3, 3.62, 5.7, 6.8–7.4 ppm.

HRMS: 533.1993

139) N-(3-(R or S)-{Cyclopropyl-[6-(1-(S)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.30 (5% methanol in dichloromethane)

^{1}H NMR δ0.2, 0.5, 0.65, 0.86, 1.63, 1.80, 2.51, 2.8, 3.3, 3.62, 5.7, 6.8–7.4 ppm.

HRMS: 533.1993

140) N-(3-(R or S)-{Cyclopropyl-[6-(1-(S)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.30 (5% methanol in dichloromethane)

^{1}H NMR δ0.17, 0.44, 0.62, 0.83, 1.6, 1.75, 2.50, 2.7–3.0, 3.3, 3.53, 5.80, 6.9–7.4 ppm.

HRMS: 533.1990

141) N-(3-(R or S)-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide

Physical characteristics are as follows:

TLC R_f 0.34 (30% ethyl acetate in dichloromethane)

^{1}H NMR δ0.2, 0.45, 0.6, 0.86, 1.5–1.9, 2.5, 2.8–3.0, 3.2, 5.7, 6.9–7.4, 7.8, 8.6 ppm.

MS: 530

142) N-(3-(R or S)-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide

Physical characteristics are as follows:

TLC R_f 0.35 (30% ethyl acetate in dichloromethane)

^{1}H NMR δ0.11, 0.20, 0.43, 0.58, 0.85, 1.5–1.8, 2.5, 2.7–3.0, 3.3, 5.69, 6.9–7.4, 7.8, 8.6 ppm.

MS: 530

143) N-(3-(R or S)-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-2-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.34 (5% methanol in dichloromethane)

^{1}H NMR δ0.19, 0.5, 0.65, 0.89, 1.6–1.9, 2.5, 2.8–3.0, 3.3, 3.40, 5.70, 6.8–7.4 ppm.

MS: 533

144) N-(3-(R or S)-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-2-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.34 (5% methanol in dichloromethane)

^{1}H NMR δ0.20, 0.44, 0.65, 0.88, 1.6–1.8, 2.5, 2.8–3.0, 3.3, 3.42, 5.73, 6.8–7.4 ppm.

MS: 533

145) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-2-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.22 (5% methanol in dichloromethane)

^{1}H NMR δ0.16, 0.24, 0.47, 0.64, 0.86, 1.2–1.9, 3.2–3.4, 3.47, 3.7–4.0, 5.89, 6.9–7.4 ppm.

MS: 541

145A) N-(3-[Cyclopropyl[4-hydroxy-2-oxo-6-[1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-3-yl]methyl]phenyl]-8-quinolinesulfonamide

Physical characteristics are as follows:

MW Found: m/z 588.

145B) N-(3-[Cyclopropyl[4-hydroxy-2-oxo-6-[1-[(tetrahydro-2H-pyran-3-yl)methyl]propyl]-2H-pyran-3-yl]methyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide

Physical characteristics are as follows:

MW Found: m/z 541.

146) N-(3-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-benzimidazole-2-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.40 (50% ethyl acetate in dichloromethane)

^{1}H NMR δ0.1–0.6, 0.85, 1.5–1.7, 2.5, 2.7–3.0, 3.3, 5.74, 6.7–7.3, 7.5–7.7 ppm.

HRMS: 570.2054

147) N-(3-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-imidazole-2-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.31 (5% methanol in dichloromethane)

^{1}H NMR δ0.2, 0.4, 0.6, 0.87, 1.5–1.8, 2.5, 2.8–3.0, 3.3, 5.54, 6.8, 6.9–7.4 ppm.

148) N-(3-(R or S)-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-4-cyanobenzenesulfonamide

Physical characteristics are as follows:

TLC R_f 0.47 (20% ethyl acetate in dichloromethane)

^{1}H NMR δ0.1, 0.2, 0.4, 0.6, 0.84, 1.5–1.8, 2.5, 2.7–3.0, 3.3, 5.70, 6.9, 7.0–7.3, 7.6, 7.8 ppm.

HRMS: 554.1886

149) N-(3-(R or S)-{Cyclopropyl-[6-(1-(R)-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-4-cyanobenzenesulfonamide

Physical characteristics are as follows:

TLC R_f 0.35 (15% ethyl acetate in dichloromethane)

^{1}H NMR δ0.1, 0.2, 0.4, 0.6, 0.85, 1.5–1.9, 2.5, 2.7–3.0, 3.3, 5.7, 6.9–7.3, 7.6, 7.8 ppm.

HRMS: 554.1876

150) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-4-nitrobenzenesulfonamide

Physical characteristics are as follows:

TLC R_f 0.28 (10% ethyl acetate in dichloromethane)

^{1}H NMR δ0.1, 0.2, 0.4, 0.6, 0.83, 1.5–1.9, 2.5, 2.7–3.0, 3.3, 5.70, 6.9–7.3, 7.9, 8.2 ppm.

HRMS: 574.1773

PREPARATION 55

(2-(2-(2-Methoxyethoxy)-ethoxy)-ethoxy)-p-toluenesulfonate (Formula M-2) Refer to Chart M

To a stirred suspension of 19.1 g of p-toluenesulfonyl chloride in 100 ml of dichloromethane is added a mixture of 16 ml of triethylene glycol monomethyl ether and 10 ml of pyridine, followed by 200 mg of dimethylaminopyridine. After three days the mixture is concentrated under reduced pressure, and the residue partitioned between ethyl acetate and dilute aqueous hydrochloric acid. The organic phase is washed with water, aqueous sodium bicarbonate, and brine, and dried over magnesium sulfate. After removal of solvent under reduced pressure, the residue is flash chromatographed on silica using 25% ethyl acetate in dichloromethane to afford 18.25 g of the title compound as a colorless liquid.

Physical characteristics are as follows:

TLC R_f 0.27 (20% ethyl acetate in dichloromethane)

^{1}H NMR δ2.45, 3.38, 3.5–3.8, 4.15, 7.35, 7.8 ppm.

IR 2879, 1357, 1190, 1177, 1108, 1099, 924, 665 cm^{-1}

MS: 318

PREPARATION 56

2-Hydroxy-4-(2-(2-(2-methoxyethoxy)-ethoxy)-ethoxy)-acetophenone (Formula M-3) Refer to Chart M

A mixture of 1.52 g of 2,4-dihydroxyacetophenone, 3.82 g of the tosylate of Preparation 55, 3.26 g of cesium carbonate, and 0.2 g of potassium iodide in 20 ml of dioxane is heated overnight at 100°, then cooled and partitioned between dichloromethane and dilute aqueous hydrochloric

acid. The aqueous phase is extracted with two additional portions of dichloromethane, and the combined organic phase dried over magnesium sulfate and then concentrated under reduced pressure. Flash chromatography of the residue on silica gel using 80–100% ethyl acetate in hexane provides 2.91 g of the title compound as a nearly colorless liquid.

Physical characteristics are as follows:

TLC R_f 0.35 (80% ethyl acetate in hexane)

^{1}H NMR δ2.56, 3.38, 3.5–3.9, 4.2, 6.4–6.5, 7.6 ppm.

IR 1635, 1372, 1257, 1133 cm^{-1}

MS: 298

PREPARATION 57

3-(2-Hydroxy-4-(2-(2-(2-methoxyethoxy)-ethoxy)-ethoxy)-phenyl-3-oxopropionic acid ethyl ester (Formula M-4) Refer to Chart M

To a stirred solution of 1.49 g of the title compound of Preparation 56 in 10 ml of diethyl carbonate is added, in portions, 600 mg of 60% sodium hydride dispersion in mineral oil. The resulting mixture is heated at 80° for two hours, then cooled and partitioned between dichloromethane and dilute aqueous hydrochloric acid. The organic phase is dried over magnesium sulfate and concentrated under reduced pressure, and the residue purified by flash chromatography on silica gel using 20–30% ethyl acetate in dichloromethane to afford 0.91 g of the title compound as a yellow oil.

Physical characteristics are as follows:

TLC R_f 0.44 (3% acetic acid and 30% ethyl acetate in dichloromethane)

^{1}H NMR δ1.3, 3.38, 3.5–4.0, 4.2, 6.4–6.5, 7.6 ppm.

MS: 370

PREPARATION 58

4-Hydroxy-(2-(2-(2-methoxyethoxy)-ethoxy)-ethoxy)-coumarin (Formula M-5) Refer to Chart M

A solution of 789 mg of the title compound of Preparation 57 in 10 ml of acetic acid is refluxed for two hours, then concentrated under reduced pressure. Flash chromatography of the residue on silica using 5–10% acetic acid in ethyl acetate provides 634 mg of the title compound as a buff colored solid.

Physical characteristics are as follows:

TLC R_f 0.31 (10% acetic acid in ethyl acetate)

^{1}H NMR δ3.37, 3.5–3.9, 4.1, 5.67, 6.6, 6.7, 7.6 ppm.

MS: 324

PREPARATION 59

3-[(3-Benzyloxycarbonylaminophenyl)-cyclopropylmethyl]-4-hydroxy-7-{2-[2-(2-methoxyethoxy)-ethoxy]-ethoxy}-coumarin (Formula M-6) Refer to Chart M

A mixture of 704 mg of the title compound of Preparation 58, 775 mg of meta-benzyloxycarbonylaminophenyl cyclopropyl carbinol of formula F-5, and 62 mg of p-toluenesulfonic acid monohydrate in 8 ml of dichloromethane is refluxed for 18 hours through ca. 10 ml of 3 Å sieves. The solution is then concentrated under reduced pressure and the residue flash chromatographed on silica gel using 10–20% of (10% acetic acid in ethyl acetate) in dichloromethane to afford 760 mg of the title compound.

Physical characteristics are as follows:

TLC R_f 0.33 (2% acetic acid and 20% ethyl acetate in dichloromethane)

^{1}H NMR δ0.27, 0.46, 0.71, 1.61, 3.33, 3.5–3.9, 4.1, 5.13, 6.6, 6.7, 7.1–7.6 ppm.

PREPARATION 60

3-[(3-Aminophenyl)-cyclopropylmethyl]-4-hydroxy-7-{2-[2-(2-methoxyethoxy)-ethoxy]-ethoxy}-coumarin (Formula M-7) Refer to Chart M

A solution of 760 mg of the title compound of Preparation 59, 800 mg of ammonium formate, and 200 mg of 5% palladium on charcoal catalyst in 8 ml of methanol is stirred under argon for one hour, then filtered through a pad of diatomaceous earth. The filtrate is concentrated under reduced pressure and the residue triturated with dichloromethane. Removal of solvent under reduced pressure provides 591 mg of the title amine.

Physical characteristics are as follows:

TLC R_f 0.29 (5% methanol in dichloromethane)

EXAMPLE 151

N-(3-{Cyclopropyl-[7-(2-(2-(2-methoxyethoxy)-ethoxy) ethoxy)-4-hydroxycoumarin-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole- 4-sulfonamide (Formula M-8) Refer to Chart M

To a stirred solution of 70 mg of the title compound of Preparation 60 and 24 μL of pyridine in 0.5 ml of dichloromethane is added 27 mg of 1-methylimidazole-4-sulfonyl chloride. After 18 hours, the solution is flash chromatographed on silica gel using 5–15% methanol in dichloromethane, affording 76 mg of the title sulfonamide as a pink amorphous foam.

Physical characteristics are as follows:

TLC R_f 0.21 (5% methanol in dichloromethane)

^{1}H NMR δ0.16, 0.29, 0.45, 0.61, 1.71, 3.34, 3.4–3.9, 4.1, 6.6–6.8, 7.0–7.4, 7.7 ppm.

HRMS: 614.2179

EXAMPLES 152–154

Utilizing procedures analogous to those described above, the following additional compounds of the present invention are prepared:

152) N-(3-{Cyclopropyl-[7-methoxy-4-hydroxycoumarin-3-yl]-methyl}-phenyl)-1-methyl-1H-imidazole-4-sulfonamide

Physical characteristics are as follows:

TLC R_f 0.29 (5% methanol in dichloromethane)

^{1}H NMR δ0.18, 0.35, 0.50, 0.63, 1.61, 3.51, 3.7, 3.84, 6.7–6.8, 7.1–7.4, 7.7 ppm.

HRMS: 481.1301

153) N-(3-{Cyclopropyl-[7-(2-(2-(2-methoxyethoxy)-ethoxy)ethoxy)-4-hydroxycoumarin-3-yl]-methyl}-phenyl)-8-quinolinesulfonamide

Physical characteristics are as follows:

TLC R_f 0.41 (5% methanol in dichloromethane)

^{1}H NMR δ–0.03, 0.31, 0.47, 1.30, 3.36, 3.5–3.8, 3.9, 4.2, 6.6–7.6, 7.8, 8.0, 8.2 ppm.

HRMS: 661.2219

154) N-(3-{Cyclopropyl-[7-(2-(2-(2-methoxyethoxy)-ethoxy)ethoxy)-4-hydroxycoumarin-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide

Physical characteristics are as follows:

TLC R_f 0.31 (5% methanol in dichloromethane)

^{1}H NMR δ0.13, 0.34, 0.49, 0.63, 1.6, 3.36, 3.5–3.9, 4.1, 6.68, 6.8, 7.1–7.4, 7.6–7.8, 8.5 ppm.

HRMS: 611.2051

EXAMPLES 155–190

The following additional compounds of the present invention are prepared by procedures analogous to those described above:

155) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide

156) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-4-cyano-2-pyridinesulfonamide

157) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-quinolinesulfonamide

158) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-hydroxybenzenesulfonamide

159) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyrazolesulfonamide

160) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-quinazolinesulfonamide

161) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-7H-purine-6-sulfonamide

162) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-imidazole-2-sulfonamide

163) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-benzimidazole-2-sulfonamide

164) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-thiazole-4-sulfonamide

165) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-4-ethoxycarbonyl-1H-imidazole-2-sulfaonamide

166) N-(3-{Cyclopropyl-[6-(1-(tetrahydropyran-4-ylmethyl)-propyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-3-hydroxy-2-pyridinesulfonamide

167) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide

168) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-4-cyano-2-pyridinesulfonamide

169) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-quinolinesulfonamide

170) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-hydroxybenzenesulfonamide

171) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-pyrazolesulfonamide

172) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-2-quinazolinesulfonamide

173) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-7H-purine-6-sulfonamide

174) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-1H-imidazole-2-sulfonamide

175) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-benzimidazole-2-sulfonamide

176) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-thiazole-4-sulfonamide

177) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-4-ethoxycarbonyl-1H-imidazole-2-sulfaonamide

178) N-(3-{Cyclopropyl-[6-(1-ethylphenethyl)-4-hydroxy-2-oxo-2H-pyran-3-yl]-methyl}-phenyl)-3-hydroxy-2-pyridinesulfonamide

179) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-2-pyridinesulfonamide

180) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-4-cyano-2-pyridinesulfonamide

181) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-2-quinolinesulfonamide

182) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-2-hydroxybenzenesulfonamide

183) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-2-pyrazolesulfonamide

184) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-2-quinazolinesulfonamide

185) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-7H-purine-6-sulfonamide

186) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-1H-imidazole-2-sulfonamide

187) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-benzimidazole-2-sulfonamide

188) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-thiazole-4-sulfonamide

189) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-4-ethoxycarbonyl-1H-imidazole-2-sulfaonamide

190) N-(3-{Cyclopropyl-[4-hydroxycoumarin-3-yl]-methyl}-phenyl)-3-hydroxy-2-pyridinesulfonamide

PREPARATION 61

Cyclopropyl-(3-nitrophenyl)methanone (Formula N-2) Refer to Chart N

Charge a jacketed 1 L three neck round bottom flask equipped with stirrer and addition funnel under nitrogen with 580 mL fuming nitric acid and cool to −40° C. Slowly, over 1.5 hours, add cyclopropyl phenyl ketone of formula N-1 (100 g) keeping the temperature below −35° C. Stir 3 hours, monitoring reaction by TLC. Pour reaction mixture into 3 kg ice/water. Extract with 3×500 mL ethyl acetate. Wash combined organic phase with 2×1.5 L saturated aqueous sodium bicarbonate, dry over magnesium sulfate, filter and concentrate to 138 g. Dissolve residue in 270 mL methanol, cool to −20° C. for 18 hours, filter and wash cake with cold methanol. Dry product under reduced pressure for 72 hours, obtaining 63.86 g. GC analysis (15 m. DB-1, T_o=100° C., 10° C./min., RT −6.0 min.) indicates material to be >98% pure.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ8.86, 8.43, 8.34, 7.70, 2.72, 1.33, 1.17 ppm.

IR (Nujol) 2954, 2925, 1664, 1614, 1529, 1442, 1386, 1352, 1225, 1082, 1047, 852, 720, 689 cm^{-1}.

Elemental analysis, Found: C, 62.89; H, 4.73; N, 7.32.

MS (EI) 191, 150, 104, 69 m/z.

PREPARATION 62

Cyclopropyl-(3-aminophenyl)methanone (Formula N-3) Refer to Chart N

Charge platinum on carbon (8.7 g) to Paar bottle. Charge a flask with cyclopropyl(3-nitrophenyl)methanone of Preparation 61 (86.7 g) and methanol (1.56 L) and warm to dissolve, then cool with ice bath to 9° C. Hydrogenate for 50 minutes, keeping temperature below 35° C. and monitoring reaction by TLC. Filter reaction mixture through solka floc, and concentrate under reduced pressure to 70 g.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.99, 7.47–7.19, 6.84, 3.84, 2.60, 1.23–1.15, 1.03–0.96 ppm.

^{13}C NMR ($CDCl_3$) δ200.9, 146.8, 139.1, 129.4, 119.3, 118.4, 113.9, 17.2, 11.6 ppm.

PREPARATION 63

Cyclopropyl-(3-aminocarbobenzoxyphenyl)methanone (Formula N-4) Refer to Chart N

Charge a 3 L round bottom flask equipped with mechanical stirrer and addition funnel under nitrogen with cyclopropyl-(3-aminophenyl)methanone of Preparation 62 (70.0 g), diisopropylethylamine (DIPEA, 90.2 mL) and methylene chloride (CH_2Cl_2) (1.3 L). Cool reaction mixture to 0° C. Dilute the benzylchloroformate (67.5 mL) with methylene chloride (186 mL) and add to the substrate solution over one hour keeping temperature at 0°–5° C. A heavy precipitate will form. Allow to warm with stirring for 1.5 hours monitoring reaction by TLC. Pour reaction mixture into 600 mL 1N HCl/600 g ice/4.2 L methylene chloride and stir to dissolve. Separate phases and dry organic phase over magnesium sulfate, filter and concentrate to a dryness. Slurry solids in 3 mL/g hexane, filter, and vacuum dry for 125 g.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ8.01, 7.76–7.69, 7.43–7.33, 7.18, 5.21, 2.64, 1.25–1.20, 1.03–0.97 ppm.

^{13}C NMR ($CDCl_3$) δ200.6, 153.4, 138.7, 138.5, 135.9, 129.3, 128.6, 128.4, 123.1, 122.8, 118.1, 67.2, 17.3, 12.0 ppm.

PREPARATION 64

Cyclopropyl-(3-aminocarbobenzoxyphenyl)methanol (Formula N-5) Refer to Chart N

Charge a 2 L three neck round bottom flask equipped with overhead stirrer under nitrogen with cyclopropyl-(3-aminocarbobenzoxyphenyl)methanone of Preparation 63 (25 g), tetrahydrofuran (THF) (450 mL) and ethanol (90 mL). Cool reaction mixture to 0°–5° C. and add the sodium borohydride pellets (12.4 g) in three equal portions over 30 minutes. Allow to warm to 23° C. and stir for 20 hours, monitoring reaction by TLC. Recool reaction mixture to 0°–5° C. and slowly quench by adding 90 mL 1N hydrochloric acid, keeping the temperature below 10° C. Pour with stirring into methylene chloride (600 mL) and 1N hydrochloric acid (400 mL). Separate the phases and wash the organic phase with saturated sodium chloride solution (1 L). Dry over magnesium sulfate, filter, and concentrate to 23.7 g.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.41–7.35, 7.33, 7.17, 7.10, 5.17, 3.93, 2.36, 1.16–1.12, 0.60–0.32 ppm.

^{13}C NMR ($CDCl_3$) δ153.5, 145.0, 137.9, 136.1, 129.0, 128.6, 128.3, 121.2, 117.9, 116.5, 67.9, 67.0, 19.1, 3.6, 2.8 ppm.

PREPARATION 65

Carbamic acid, [3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-, phenylmethyl ester (Formula N-6) Refer to Chart N

A 12-L, three-necked, round-bottomed flask with a Soxhlet extractor containing 3 Å molecular sieves (180 g) and nitrogen inlet is charged with cyclooctene-1-acrylic acid, β, 2-dihydroxy-δ-lactone (59.6 g), p-toluenesulfonic acid (14.9 g), and methylene chloride (7.2 L). The title compound of Preparation 64 (90.0 g) is added, and the reaction mixture is warmed to reflux for 1 h. The reaction mixture is then cooled to 20° C. and washed with 1:1 saturated sodium chloride/saturated sodium bicarbonate (3 L), water (3 L), and saturated sodium chloride (3 L), backwashing each aqueous phase with methylene chloride (2×1.5 L). The organic layers are then combined, dried over magnesium sulfate, filtered and concentrated to ca. 1.5 L. The reaction mixture is cooled to −20° C. for 72 h, filtered, and dried under reduced pressure to give 103.5 g. The crude product is then slurried with 12.5 mL/g of hexane, filtered, and dried to give 102.4 g of the title compound. An additional 10.9 g of the title compound is obtained by concentrating the mother liquors from the crystallization and recrystallizing the residue from ethyl acetate.

Physical characteristics are as follows:

MP 113°–115° C. (decomposition).

^{1}H NMR ($CDCl_3$) δ7.48, 7.38–7.26, 7.17, 6.70, 6.29, 5.20, 3.95, 2.64–2.60, 2.47–2.43, 1.76–1.72, 1.61–1.42, 0.88, 0.73–0.72, 0.63–0.55, 0.29–0.26 ppm.

^{13}C NMR ($CDCl_3$) δ165.6, 164.0, 161.3, 142.2, 138.5, 129.9, 128.5, 128.3, 128.2, 122.9, 118.0, 117.9, 117.6, 110.7, 106.0, 67.0, 43.7, 30.7, 29.1, 28.8, 26.2, 25.8, 22.1, 13.0, 4.9, 3.8 ppm.

IR (Nujol) 3304, 2995, 2953, 2923, 2855, 1734, 1698, 1665, 1666, 1633, 1610, 1595, 1553, 1491, 1463, 1455, 1445, 1406, 1377, 1313, 1222, 1175, 1085, 1068, 740, 696 cm^{-1}.

MS (EI) m/z 473, 445, 382, 338, 91.

For high resolution, Found: 473.2202.

PREPARATION 66

3-[(3-Aminophenyl)cyclopropylmethyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one (Formula N-7) Refer to Chart N

In a 100-mL, three-necked, round-bottomed flask with a reflux condensor and nitrogen inlet, 10% palladium on carbon (1.0 g) is added to a mixture of the title product of formula N-6, prepared in Preparation 65 (1.95 g) in cyclohexene (50 mL) and the mixture is refluxed for 4 h. The mixture is then filtered through Celite, washed with methylene chloride (CH_2Cl_2), and concentrated to give 1.25 g of the title compound as a white solid.

Physical characteristics are as follows:

MP 75°–79° C.

IR (Nujol) 2995, 2951, 2921, 2868, 1660, 1619, 1605, 1590, 1551, 1491, 1460, 1447, 1428, 1404, 1247, 1226, 1202, 1191, 1172, 1126 cm^{-1}.

MS (EI) m/z 339, 310, 213, 187, 159.

^{1}H NMR ($CDCl_3$) δ7.16, 6.96, 6.84, 6.63, 5.67, 3.87, 2.61, 2.48–2.37, 1.98, 1.75, 1.63–1.26, 0.74–0.65, 0.61–0.53, 0.28–0.22 ppm.

^{13}C NMR ($CDCl_3$) δ164.2, 161.1, 142.8, 130.2, 117.7, 117.6, 114.7, 114.6, 114.5, 110.9, 106.2, 43.5, 30.6, 29.1, 28.8, 26.2, 25.8, 22.0, 12.8, 4.7, 3.7 ppm.

For high resolution, Found: 339.1845.

PREPARATION 67

4-Cyano-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide (Formula O-3 wherein R_{61} is 4-cyanophenyl) Refer to Chart O

A solution of the title product of Preparation 66 (660 mg), pyridine (320 μL), and 4-cyanobenzenesulfonyl chloride (440 mg) in dichloromethane (40 mL) is stirred at room temperature for 18 hr. The crude reaction mixture is evaporated to a volume of 5 ml and chromatographed on silica gel using 50% ethyl acetate in hexane as eluent to give the title compound (641 mg) as a white amorphous solid. This amorphous solid is alternatively crystallized from acetone:hexane to give 499 mg.

Physical characteristics are as follows:

White solid mp: 183°–183.5° C.

Elemental analysis: found, C, 66.76; H, 5.68; N, 5.38; s, 6.30.

MS(EI): 504, 476, 463, 338, 309, 233, 220, 207, 195, 186, 153, 144, 130, 117, 102.

HRMS: 504.1710.

TLC(silica gel GF): R_f=0.4 in 50% ethyl acetate in hexane.

EXAMPLE 191

Disodium-4-cyano-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl) methyl]phenyl]-benzenesulfonamide

To 12.6 g of the title product of Preparation 67 is added 500 ml of methanol and, with rapid stirring, 50 ml of a 1N aqueous NaOH solution. The reaction solution is allowed to stir at room temperature for 1 hour. The yellow solution is evaporated to dryness at 35° C. and the resulting amorphous residue is dissolved in absolute ethanol and re-evaporated to dryness. The yellow residue is kept under high vacuum at room temperature for 18 hours to yield 14 g of a yellow amorphous solid.

Physical characteristics are as follows:

TLC(silica gel GF): R_f=0.8 streak from the origin (20% ethylacetate in methylene chloride)

K.F. Water: 6.16%

Melt Solvate: 4.2% ethanol

Weight Loss at Room Temperature: 4.99%

Ash: found: 7.83%; Calc'd: 7.50% (corrected for 6.16% water and 4.2% ethanol)

PREPARATION 68

N-methyl-3[(3-aminophenyl)cyclopropylmethyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

To 678 mg of the title product of Preparation 66 is added 100 ml of absolute ethanol and 330 mg of 10% Pd/C. 183 microliters of a 35% CH_2O/H_2O solution is added and the mixture allowed to shake on a Paar apparatus, under 50 lbs of hydrogen, for 2 hours at room temperature. The reaction is filtered over celite and the filter cake is washed well with ethanol. The resulting amber solution is evaporated to dryness. The resulting residue is chromatographed using 10% ethyl acetate in methylene chloride to give 110 mg of the title product. This material is used without further purification in the synthesis of the following sulfonamides.

Physical characteristics are as follows:

TLC(silica gel GF): R_f=0.5 in 10% ethyl acetate in methylene chloride.

^{1}H NMR ($CDCl_3$) δ7.19, 6.90, 6.71, 6.54–6.52, 3.90, 2.80, 2.63–2.59, 2.43–2.39, 1.75–1.26, 0.70–0.53, 0.28–0.22 ppm.

EXAMPLE 192

4-Cyano-N-methyl-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl) methyl]phenyl]-benzenesulfonamide

A solution of the title compound of Preparation 68 (35 mg), pyridine (16 μL), and 4-cyanobenzenesulfonyl chloride (20.1 mg) in dichloromethane (2 mL) is stirred at room temperature for 18 hr. The crude reaction mixture is chromatographed on silica gel using 10% ethyl acetate in methylene chloride as eluent to give 27 mg of the title compound as a white amorphous solid.

Physical characteristics are as follows:

MS(EI): 518, 490, 352, 233, 207, 172, 158, 143, 129, 115, 102, 81, 54, 43.

TLC(silica gel GF): R_f=0.7 in 10% ethyl acetate in methylene chloride.

^{1}H NMR ($CDCl_3$) δ7.75–7.72, 7.63–7.60, 7.38–7.19, 6.97–6.94, 6.62, 3.86, 3.19, 2.66–2.62, 2.54–2.50, 1.76–1.20, 0.70–0.59, 0.47–42, 0.24–0.19 ppm.

EXAMPLE 193

4-Fluoro-N-methyl-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl) methyl]phenyl]-benzenesulfonamide

A solution of the title compound of Preparation 68 (20 mg), pyridine (11 μL), and 4-fluorobenzenesulfonyl chloride (10.7 mg) in dichloromethane (2 mL) is stirred at room temperature for 18 hr. The crude reaction mixture is chromatographed on silica gel using 10% ethyl acetate in methylene chloride as eluent to give 19 mg of the title compound as a white amorphous solid.

Physical characteristics are as follows:

MS(EI): 512, 483, 470, 366, 352, 324, 247, 227, 207, 172, 158, 147, 118, 55.

HRMS: Found: 512.1915

TLC(silica gel GF): R_f=0.7 in 10% ethyl acetate in methylene chloride.

^{1}H NMR ($CDCl_3$) δ7.53–7.48, 7.33–7.23, 7.13–7.07, 6.99–6.97, 6.38, 3.93, 3.16, 2.63–2.61, 2.49–2.46, 1.76–1.25, 0.78–0.61, 0.51–0.45, 0.30–0.17 ppm.

EXAMPLE 194

N-methyl-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide

A solution of the title compound of Preparation 68 (33.4 mg), pyridine (16 μL), and benzenesulfonyl chloride (16.6 mg) in dichloromethane (2 mL) is stirred at room temperature for 18 hr. The crude reaction mixture was chromatographed on silica gel using 10% ethyl acetate in methylene chloride as eluent to give 20 mg of the title compound as a white amorphous solid.

Physical characteristics are as follows:

TLC(silica gel GF): R_f=0.7 in 10% ethyl acetate in methylene chloride.

^{1}H NMR ($CDCl_3$) δ7.59–7.41, 7.33–7.23, 6.98–6.96, 6.44, 3.90, 3.16, 2.64–2.60, 2.50–2.48, 1.75–1.20, 0.67–0.40, 0.23–0.20 ppm.

EXAMPLE 195

N-methyl-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-1H-Imidazole-1-methyl-sulfonamide

A solution of the title compound of Preparation 68 (33.4 mg), pyridine (16 μL), and N-methyl-imidazole-3-sulfonyl chloride (16 mg) in dichloromethane (2 mL) is stirred at room temperature for 18 hr. The crude reaction mixture is chromatographed on silica gel using 50% ethyl acetate in methylene chloride as eluent to give 28 mg of the title compound as a white amorphous solid.

Physical characteristics are as follows:

TLC(silica gel GF): R_f=0.5 in 50% ethyl acetate in methylene chloride.

^{1}H NMR ($CDCl_3$) δ7.43, 7.33, 7.27–7.15, 3.84–3.81, 3.69, 3.35, 2.63–2.59, 2.50–2.46, 1.75–1.26, 0.68, 0.55, 0.47–0.42, 0.24–0.20 ppm.

Utilizing procedures analogous to those described above, the following compounds of the present invention are prepared:

196) 5-cyano-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-2-pyridinesulfonamide

197) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-2-quinolinesulfonamide

198) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-2-imidazolesulfonamide

199) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-2-pyrimidinesulfonamide

200) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-2-benzimidazolesulfonamide

201) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-2-quinazolinesulfonamide

202) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-6-purinesulfonamide

203) 5-cyano-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-N-methyl-2-pyridinesulfonamide

204) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-N-methyl-2-quinolinesulfonamide

205) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-N-methyl-2-imidazolesulfonamide

206) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-N-methyl-2-pyrimidinesulfonamide

207) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-2-benzimidazolesulfonamide

208) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-2-quinazolinesulfonamide

209) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-N-methyl-6-purinesulfonamide

210) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-N-methyl-4-thiazolesulfonamide

211) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl] phenyl]-N-methyl-2-pyridinesulfonamide

212) 5-cyano-N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-pyridinesulfonamide

213) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-quinolinesulfonamide

214) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-imidazolesulfonamide

215) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-pyrimidinesulfonamide

216) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-benzimidazolesulfonamide

217) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-quinazolinesulfonamide

218) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-6-purinesulfonamide

219) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-4-thiazolesulfonamide

220) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-pyridinesulfonamide

221) 5-cyano-N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-pyridinesulfonamide

222) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-quinolinesulfonamide

223) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-imidazolesulfonamide

224) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-pyrimidinesulfonamide

225) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-benzimidazolesulfonamide

226) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-quinazolinesulfonamide

227) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-6-purinesulfonamide

228) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-4-thiazolesulfonamide

229) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-pyridinesulfonamide

230) 5-cyano-N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-pyridinesulfonamide

231) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-quinolinesulfonamide

232) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-imidazolesulfonamide

233) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-pyrimidinesulfonamide

234) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-benzimidazolesulfonamide

235) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-quinazolinesulfonamide

236) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-6-purinesulfonamide

237) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-4-thiazolesulfonamide

238) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-pyridinesulfonamide

EXAMPLE 239

2-Pyridylsulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl) methyl]phenyl]-(Formula P-2, R is 2-pyridyl) Refer to Chart P

3-[(3-Aminophenyl)cyclopropylmethyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one of Preparation 66 (100 mg) is dissolved in methylene chloride (3 mL) and pyridine (70 μL) added. 2-Pyridylsulfonyl chlo-

ride (52 mg) is added and the solution stirred for 2 hr at 25° C. Chloroform (25 mL) is added and the combined extracts washed with 1N.HCl (20 mL) and dried over sodium sulfate. Removal of the solvent gives a pink gum which is chromatographed over silica gel using the flash column technique eluting with 60% ethyl acetate-hexane. The title compound is obtained as a white solid (80 mg).

Physical characteristics are as follows:

MS m/z 480, 339, 338, 186, 145, 144, 132, 130, 78, 55.

EXAMPLE 240

4-Pyridylsulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl) methyl]phenyl]-(Formula P-2, R is 4-pyridyl) Refer to Chart P

Using procedures described in Example 239, the title compound is obtained as a white solid.

Physical characteristics are as follows:

MS m/z 480, 338, 207, 186, 145, 144, 117, 79, 78, 55

EXAMPLE 241

5-Cyanopyridin-2-yl-sulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-(Formula P-2, R is 5-cyanopyridin-2-yl) Refer to Chart P

The title compound is prepared using procedures described in Example 239.

EXAMPLE 242

2-Pyrazinylsulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl) methyl]phenyl]-(Formula P-2, R is 2-pyrazinyl) Refer to Chart P

The title compound is prepared using procedures described in Example 239.

EXAMPLE 243

2-Pyrimidinylsulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl) methyl]phenyl]-(Formula P-2, R is 2-pyrimidinyl) Refer to Chart P

The title compound is prepared using procedures described in Example 239.

EXAMPLE 244

4-6-Dimethylpyrimidin-2-yl-sulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-(Formula P-2, R is 4,6-dimethylpyrimidin-2-yl) Refer to Chart P

The title compound is prepared using procedures described in Example 239.

EXAMPLE 245

4-Methylpyrimidin-2-yl-sulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b] pyran-3-yl)methyl]phenyl]-(Formula P-2, R is 4-methylpyrimidin-2-yl) Refer to Chart P

The title compound is prepared using procedures described in Example 239.

PREPARATION 69

6,6-Bis-(2-cyclopropyl-ethyl)-dihydro-pyran-2,4-dione (Formula Q-2) Refer to Chart Q

To a suspension of 150 mg of sodium hydride (60% dispersion in mineral oil) in 4 ml of dry THF under argon atmosphere at 0° C. is added dropwise 0.38 ml of methyl acetoacetate. After 10 minutes 2.3 ml of butyllithium (1.6M in hexanes) is added. After 10 minutes a solution of 0.48 g of the compound of formula Q-1 (prepared as described in Preparation 79 (Formula S-4, refer to Chart S)) in 3 ml of tetrahydrofuran is added. The reaction mixture is stirred for 1 hour, then partitioned between ethyl acetate and dilute aqueous hydrogen chloride. The aqueous phase is extracted with two additional portions of ethyl acetate. The organic phases are combined, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue is diluted with 5 mL of methanol and the resulting solution treated with 12 mL of water followed by 3.0 ml of 1M aqueous sodium hydroxide. After 2 hours of vigorous stirring the methanol is removed under reduced pressure. The aqueous phase is washed once with diethyl ether; the ether phase is discarded. The aqueous phase is cooled to 0° C., then acidified with dilute aqueous hydrogen chloride. The resulting precipitate is extracted with four portions of dichloromethane. The combined dichloromethane extracts are dried over magnesium sulfate and concentrated under reduced pressure. The residue is dissolved in diethyl ether-hexane and the solution is chilled to provide to provide 0.42 g of the title compound as a pale yellow solid.

Physical characteristics are as follows:

^{1}H NMR δ0.0, 0.4, 0.6, 1.2, 1.7, 2.6, 3.4.

PREPARATION 70

6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)-propyl]-pyran-2-one (Formula Q-3) Refer to Chart Q

To a stirred solution of 0.41 g of the title compound of Preparation 69 (Formula Q-2) and 0.25 g of the 3-nitrobenzaldehyde in 5 ml of dry tetrahydrofuran is added a solution of 0.44 g of aluminum trichloride in 4.5 ml of tetrahydrofuran. After 2 hours, the reaction mixture is treated with 1.0 g of sodium carbonate decahydrate, stirred 10 minutes, diluted with diethyl ether and finally charged with magnesium sulfate. The resulting mixture is filtered through a pad of Celite with diethyl ether rinses. The filtrates are combined and concentrated under reduced pressure. The resulting residue is charged with 103 mg of copper (I) bromide-dimethyl sulfide complex and 5 ml of dry tetrahydrofuran under an argon atmosphere. The reaction mixture is treated dropwise with 2.5 mL of triethyl aluminum (1.0M in hexane) over 1.5 hours. The reaction is then slowly treated with ice and partitioned between diethyl ether and dilute aqueous hydrogen chloride. The aqueous phase is extracted with three additional portions of diethyl ether. The combined ether extracts are washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel using 20% to 40% ethyl acetate in hexane affords 0.44 g of the title compound as a tan foam.

Physical characteristics are as follows:

^{1}H NMR δ0.0, 0.4, 0.6, 1.0, 1.2, 1.7–1.9, 2.0–2.4, 2.6, 4.2, 7.5, 7.8, 8.1, 8.3

PREPARATION 71

3-[1-(3-Amino-phenyl)-propyl]-6,6-bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-pyran-2-one (Formula Q-4) Refer to Chart Q

To a solution of 0.44 g of the title compound of Preparation 70 (Formula Q-3) in 6 ml of methanol is added 0.65 g of ammonium formate and 50 mg of 10% palladium on carbon. The black slurry is stirred under argon for 3 hours, then filtered through pad of Celite with methanol washes. The filtrates are combined and the solvent is removed under reduced pressure. The residue is triturated with four portions of dichloromethane. The combined dichloromethane washes

are concentrated under reduced pressure to provide 0.37 g of the title compound as a white foam.

Physical characteristics are as follows:

R_f 0.08 (50% diethyl ether in hexane)

EXAMPLE 246

N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula Q-5: R_1 is 1-methylimidazol-4-yl) Refer to Chart Q

To a flask containing 57 mg of the title compound of Preparation 71 (Formula Q-4) and 24 μl of pyridine in 1.0 ml of dichloromethane is added 27 mg of 1-methylimidazole-4-sulfonyl chloride. After 6 hours the reaction mixture is concentrated under reduced pressure. The pyridine is azeotroped thrice with toluene. The resulting residue is flash column chromatographed on silica gel using 2% to 6% methanol in dichloromethane to provide 51 mg of the title compound as a white foam.

Physical characteristics are as follows:

^{1}H NMR δ0.0, 0.4, 0.6, 0.9, 1.1–1.4, 1.7–2.2, 2.5, 3.7, 3.95, 6.9, 7.1, 7.4, 7.5

HRMS: 528.2537 (FAB)

EXAMPLE 247

N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide (Formula Q-5: R_1 is 5-cyano-2-pyridyl) Refer to Chart Q

Using the general sulfonylation procedure described in Example 246, 57 mg of the amine of Preparation 71 (Formula Q-4) is reacted with 30 mg of 5-cyanopyridine-2-sulfonyl chloride. Flash column chromatography on silica gel using 1% to 3% methanol in dichloromethane provides 62 mg of the title compound as a tan foam.

Physical characteristics are as follows:

^{1}H NMR δ0.0, 0.4, 0.6, 0.9, 1.1–1.4, 1.6–2.2, 2.5, 3.95, 6.9–7.2, 8.0, 8.2, 9.0

HRMS: 550.2370 (FAB)

PREPARATION 72

3-Aminopropiophenone (Formula R-2) Refer to Chart R

To a solution of 3-nitropropiophenone (Formula R-1) (1.79 g) in diethyl ether is added 5% Pt/C catalyst (0.20 g). The resulting suspension is placed under a hydrogen gas atmosphere and stirred for 6 hours. The reaction mixture is filtered through a pad of Celite and the pad washed with additional portions of diethyl ether. The combined filtrates are concentrated under reduced pressure to provide 1.49 g of the title compound as pale yellow, low melting solid.

Physical characteristics are as follows:

^{1}H NMR δ1.2, 3.0, 6.9, 7.2–7.4

R_f 0.45 (33% ethyl acetate in hexane)

PREPARATION 73

1-[3-(Dibenzyl-amino)-phenyl]-propan-1-one (Formula R-3) Refer to Chart R

To a solution of the title compound of Preparation 72 of Formula R-2 (1.5 g) in dichloromethane (50 mL) is added diisopropylethylamine (6.0 mL) followed by benzyl bromide (3.6 mL). After stirring for 6 hours the reaction mixture is heated to reflux overnight. The reaction mixture is cooled to room temperature, diluted with diethyl ether (50 mL) and washed sequentially with dilute aqueous potassium hydrogen sulfate, water, saturated aqueous sodium bicarbonate, and brine. The organic layer is dried over sodium sulfate and concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel eluting with 5% to 20% ethyl acetate in hexane to provide 2.38 g of the title compound as pale yellow solid.

Physical characteristics are as follows:

^{1}H NMR δ1.1, 2.9, 4.7, 6.9, 7.2–7.4

Anal. Found: C, 83.88; H, 7.03; N, 4.20

MS: 329 (EI)

PREPARATION 74

6-[3-(Dibenzyl-amino)-phenyl]-dihydro-pyran-2,4-dione (Formula R-4) Refer to Chart R

Using the general procedure described in Preparation 69 for the formation of the dihyropyranone ring, the compound of Formula R-3 of Preparation 73 (1.96 g) is reacted with the dianion of methyl acetoacetate and cyclized to provide 0.76 g of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.8, 1.9, 2.6–2.9, 3.1–3.2, 4.7, 6.5–6.7, 7.1–7.4

MS: 413 (EI)

PREPARATION 75

6-[3-(Dibenzyl-amino)-phenyl]-5,6-dihydro-6-ethyl-4-hydroxy-3-[1-(3-nitro-phenyl)-propyl]-pyran-2-one (Formula R-5) Refer to Chart R

Using the general procedure described in Preparation 70, aluminum trichloride catalyzed condensation of 3-nitrobenzaldehyde with the compound of Formula R-4 of Preparation 74 (727 mg), followed by copper catalyzed conjugate addition with triethyl aluminum provides 800 mg of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.6, 1.6–2.1, 2.8, 3.4, 3.8, 4.4, 6.4–6.6, 6.8–7.4, 7.7–8.0

MS: 576 (EI)

PREPARATION 76

6-(3-Amino-phenyl)-3-[1-(3-amino-phenyl)-propyl]-6-ethyl-5,6-dihydro-4-hydroxy-pyran-2-one (Formula R-6) Refer to Chart R

Using the general procedure described in Preparation 71, catalytic hydrogenation of the compound of Formula R-5 of Preparation 75 (114 mg) with ammonium formate and Pd/C affords 61 mg of the title compound. Alternatively, the compound of Formula R-5 of Preparation 75 (114 mg) is reduced with Pd/C and hydrogen gas to give 72 mg of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.6–0.9, 1.8–2.1, 3.0, 3.8, 6.4–6.6, 6.95, 7.1

R_f 0.40 (10% methanol in dichloromethane)

EXAMPLE 248

N-(3-[1-(6-Ethyl-5,6-dihydro-4-hydroxy-6-[3-([(1-methyl-1H-imidazol- 4-yl)sulfonyl]amino)phenyl]-2-2H-pyran-3-yl)propyl]phenyl)-1-methyl-1H-imidazole-4-sulfonamide (Formula R-7: R_1 is 1-methylimidazol-4-yl) Refer to Chart R

Using the general sulfonylation procedure described in Example 246, the compound of Formula R-6 of Preparation 76 (61 mg) is reacted with 1-methylimidazole-4-sulfonyl chloride to provide 59 mg of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.3–0.7, 1.6–2.0, 3.0, 3.4–3.7, 6.7–7.5

HRMS: 655.1995 (FAB)

EXAMPLE 249

5-Cyano-N-(3-[1-(6-[3-([(5-cyano-2-pyridinyl)sulfonyl]amino)phenyl]-6-ethyl-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl)propyl]phenyl)-2-pyridinesulfonamide (Formula R-7: R is 5-cyano-2-pyridyl) Refer to Chart R

Using the general sulfonylation procedure described in Example 246, the compound of Formula R-6 of Preparation 76 (66 mg) is reacted with 5-cyano-2-pyridine sulfonyl chloride to provide 40 mg of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.3–0.9, 1.3, 1.6–1.9, 3.0, 3.7, 6.6–7.2, 7.9–8.2, 8.8–9.0

HRMS: 699.1679 (FAB)

PREPARATION 77

N-Methoxy-N-methyl-4-pentenoic amide (Formula S-2) Refer to Chart S

To a suspension of 4-pentenoic acid (Formula S-1) (2.00 g) and N,O-dimethylhydroxylamine hydrochloride (2.15 g) in dichloromethane (50 mL) at 0° C. is added diisopropylethylamine (11.5 mL) followed by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (5.60 g). After stirring overnight, the reaction mixture is concentrated under reduced pressure. The residue is partioned between dilute aqueous potassium hydrogen sulfate and diethyl ether. The aqueous phase is extracted with two additional portions of diethyl ether. The organic extracts are combined, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel eluting with 50% to 80% diethyl ether in hexane to provide 2.58 g of the title compound as a tan oil.

Physical characteristics are as follows:

^{1}H NMR δ2.3–2.6, 3.20, 3.70, 4.9–5.1, 5.75–5.95

R_f 0.17 (25% diethyl ether in hexane)

PREPARATION 78

Nona-1,8-dien-5-one (Formula S-3) Refer to Chart S

To a flame-dried flask under an argon atmosphere containing a solution of the title compound of Preparation 77 (Formula S-2) (1.45 g) in dry tetrahydrofuran (10 mL) at 0° C. is added 3-butenyl-1-magnesium bromide (20 mL, 1M solution in tetrahydrofuran. (Preparation of this Grignard reagent from magnesium metal and 4-bromo-1-butene is described in J.Org.Chem. 43:4247 (1978)). After 1 hour at 0° C., the reaction mixture is warmed to room temperature; after 1 hour at room temperature, the reaction mixture is poured into dilute aqueous potassium hydrogen sulfate and partioned against diethyl ether. The aqueous phase is extracted with three additional portions of diethyl ether. The organic extracts are combined, washed with brine, dried over sodium sulfate and carefully concentrated under reduced pressure. The resulting liquid is purified by distillation to provide 1.32 g of the title compound as a tan oil.

Physical characteristics are as follows:

^{1}H NMR δ2.3, 2.5, 5.0, 5.7–5.9

R_f 0.66 (25% diethyl ether in hexane)

PREPARATION 79

1,5-Dicyclopropyl-pentan-3-one (Formula S-4) Refer to Chart S

To a flame-dried flask under an argon atmosphere equipped with a reflux condenser containing zinc metal (8.0 g) and cuprous chloride (1.25 g) is added a solution of the title compound of Preparation 78 (Formula S-3) (1.32 g) in dry diethyl ether (10 mL). The resulting suspension is charged with diiodomethane (5.0 mL) and the reaction flask placed in 40° C. ultrasound bath (Branson 2200) and sonicated. After 2 hours heating is ceased and sonication is continued overnight. The reaction mixture is then diluted with diethyl ether (50 mL), cooled to 0° C., and treated with excess saturated aqueous ammonium chloride. After 0.25 hours of vigorous stirring, the mixture is filtered and the layers separated. The aqueous phase is extracted with two additional portions of diethyl ether. The organic extracts are combined and washed sequentially with dilute aqueous sodium thiosulfate, saturated aqueous sodium bicarbonate, brine; dried over magnesium sulfate and then carefully concentrated under reduced pressure. The resulting residue is purified by flash column chromatography on silica gel eluting with 5% to 20% diethyl ether in hexane to provide 0.48 g of the title compound as an oil.

Physical characteristics are as follows:

^{1}H NMR δ0.0, 0.4, 0.65, 1.45, 2.50

R_f 0.44 (10% diethyl ether in hexane)

PREPARATION 80

3-[2,2-Dimethyl-1-(3-nitro-phenyl)-propyl]-5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-pyran-2-one (Formula T-3) Refer to Chart T

To a flame-dried flask containing a slurry of 977 mg of activated zinc metal in 1.0 mL of dry tetrahydrofuran under an argon atmosphere is added 40 μL of 1,2-dibromoethane. The mixture is placed in 45° C. ultrasound bath (Branson 2200) and sonicated with stirring. After 10 minutes the mixture is treated with 0.25 mL of chlorotrimethylsilane (1.0M in tetrahydrofuran). After 10 minutes, the mixture is diluted with 4 mL of tetrahydrofuran and treated dropwise with 1.50 mL of 2-iodo-2-methylpropane. The mixture is stirred and sonicated at 45° C. for an additional 3 hours, then cooled to room temperature without stirring. In a separate flask 954 mg of anhydrous lithium chloride is heated in an 110° C. oil bath in vacuo for 1 hour. The LiCl flask is cooled to room temperature, placed under an argon atmosphere and charged with 1.01 g of copper (I) cyanide followed by 10 mL of tetrahydrofuran. After 15 minutes of stirring at room temperature, the LiCl—CuCN mixture is cooled to −30° C. and treated via cannula with the organozinc mixture prepared as described above in the first flask. The reaction flask is warmed from −30° C. to 0° C., stirred 10 minutes then cooled to −78° C. The preparation of this organometallic reagent is analogous to literature procedures (Org. Syn. 70:195–203 (1991)) described for related reagents.

In a separate flask a stirred solution of 1.56 g of 6-phenethyl-6-propyldihydro-pyran-2,4-dione of Formula T-2 (prepared from the compound of Formula T-1 as described in Preparation 17 above) and 915 mg of the 3-nitrobenzaldehyde in 22 mL of dry tetrahydrofuran is treated with a solution of 1.60 g of aluminum trichloride in 14 mL of tetrahydrofuran. After 2 hours, the reaction mixture is treated with 3.6 g of sodium carbonate decahydrate, stirred 5 minutes, diluted with diethyl ether and finally charged with magnesium sulfate. The resulting mixture is filtered through a pad of Celite with diethyl ether washes. The filtrates are combined and concentrated under reduced pressure. The resulting residue is charged with 9 mL of dry tetrahydrofuran under an argon atmosphere and is added via cannula to the cooled (−78° C.) organometallic reagent solution prepared as described above. After 0.5 hours the reaction mixture is warmed to 0° C. After 0.5 hours at 0° C. the reaction is poured into cold dilute ammonium chloride and the aqueous phase is made acidic with dilute aqueous hydrogen chloride. The mixture is treated with ethyl acetate and filtered through a pad of Celite with ethyl acetate washes. The layers are separated and the aqueous phase is extracted with three additional portions of ethyl acetate. The combined ethyl acetate extracts are washed with aqueous sodium thiosulfate, brine; dried over magnesium sulfate, and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel eluting with 30% to 50% ethyl acetate in hexane affords 1.73 g of the title compound as a tan foam.

Physical characteristics are as follows:

^{1}H NMR δ0.9, 1.1, 1.3, 1.6–2.0, 2.5–2.8, 4.3, 6.9–7.3, 7.8, 8.0, 8.5

HRMS: 452.2449 (FAB)

PREPARATION 81

3-[1-(3-Amino-phenyl)-2,2-dimethyl-propyl]-5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-pyran-2-one (Formula T-4) Refer to Chart T

To a solution of 1.72 g of the title compound of Preparation 80 (Formula T-3) in 25 mL of methanol is added 3.0 g of ammonium formate and 400 mg of 10% palladium on carbon. The black slurry is stirred under nitrogen for 3 hours, then filtered through pad of Celite with methanol washes. The filtrates are combined and the solvent is removed under reduced pressure. The residue is repeatedly triturated with portions of dichloromethane and the combined dichloromethane washes concentrated under reduced pressure. The residue is flash column chromatographed on silica gel eluting with 10% ethyl acetate in dichloromethane to provide 1.48 g of the title compound as a white foam.

Physical characteristics are as follows:

^{1}H NMR δ0.7–0.9, 1.1, 1.3–2.6, 4.2, 6.55, 6.9–7.3

HRMS: 422.2686 (FAB)

EXAMPLE 250

N-[3-(1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula T-5: R_1 is 1-methylimidazol-4-yl) Refer to Chart T

To a solution of 1.48 g of the title compound of Preparation 81 (Formula T-4) in 25 ml of dichloromethane at 0° C. is added 0.57 mL of pyridine followed by 632 mg of 1-methylimidazole-4-sulfonyl chloride. After 3 hours the reaction mixture is warmed to room temperature and concentrated under reduced pressure. Pyridine is azeotroped thrice with toluene. The resulting residue is flash column chromatographed on silica gel using 2% to 6% methanol in dichloromethane to provide 1.7 g of the title compound as a white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 0.97, 1.35, 1.6–2.0, 2.5–2.7, 3.6, 4.1, 6.9–7.5

HRMS: 566.2684

The individual stereoisomers of this compound are the following:

N-[3-(1(S)-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula KK-8 wherein R_4 is 1-methyl-1H-imidazol-4-yl) Refer to Chart KK;

N-[3-(1(R)-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula LL-8 wherein R_4 is 1-methyl-1H-imidazol-4-yl) Refer to Chart LL;

N-[3-(1(S)-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula MM-8 wherein R_4 is 1-methyl-1H-imidazol-4-yl) Refer to Chart MM; and

N-[3-(1(R)-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula NN-8 wherein R_4 is 1-methyl-1H-imidazol-4-yl) Refer to Chart NN.

EXAMPLE 251

5-Cyano-N-[3-(1-[5,6-dihydro-4-hydoxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide (Formula T-5: R_1 is 5-cyano-2-pyridyl) Refer to Chart T

Using the general sulfonylation procedure described in Example 250, 42 mg of the amine of Preparation 81 (Formula T-4) is reacted with 20 mg of 5-cyanopyridine-2-sulfonyl chloride. Flash column chromatography on silica gel using 1% to 3% methanol in dichloromethane provides 56 mg of the title compound as a white foam.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 0.92, 1.35, 1.6–2.0, 2.5–2.7, 4.0, 6.9–7.4, 8.0, 8.9

HRMS: 588.2532

PREPARATION 82

N-Methoxy, N-methyl 3-(4-fluorophenyl)propionamide (Formula U-2) Refer to Chart U

To a cold (0°), stirred solution of 5.0 g of 3-(4-fluorophenyl)propionic acid of Formula U-1, 3.2 g of (N,O)-dimethylhydroxylamine hydrochloride, and 11.4 ml of diisopropylethylamine in 40 ml of dichloromethane is slowly added a solution of 5.0 ml of diethyl cyanophosphonate in 10 ml of dichloromethane. After 18 hours, the solution is concentrated under reduced pressure. The residue is dissolved in ethyl acetate, and the solution washed with dilute HCl, water, aqueous sodium bicarbonate, and brine, and dried over magnesium sulfate. Removal of the solvent under reduced pressure provides 6.94 g of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ2.7, 2.9, 3.17, 3.61, 7.0, 7.2 ppm

IR 1665, 1511, 1222, 1033, 990 cm^{-1}

TLC R_f 0.34 (5% ethyl acetate in dichloromethane)

PREPARATION 83

1-(4-Fluorophenyl)-3-hexanone (Formula U-3) Refer to Chart U

A stirred solution of 4.68 g of the title compound of Preparation 82 (Formula U-2) in 25 ml of dry THF under argon is cooled to −15°, and to the solution is added 17 ml of a 1M solution of propylmagnesium chloride in ether. The resulting solid mass is warmed to 0°, kept at that temperature for 90 minutes, then partitioned between ether and cold dilute HCl. The aqueous phase is extracted with one additional portion of ether, and the combined organic phase washed with brine and dried over magnesium sulfate. Following removal of solvent by distillation at atmospheric pressure, the residue is purified by evaporative distillation (ca 160° @ 13 mmHg) to provide 3.51 g of the title compound as a colorless liquid.

Physical characteristics are as follows:

^{1}H NMR δ0.89, 1.6, 2.36, 2.7, 2.9, 6.9, 7.1 ppm

IR 2965, 1714, 1511, 1222 cm^{-1}

PREPARATION 84

5,6-Dihydro-4-hydroxy-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-2-one (Formula U-4) Refer to Chart U

To a cold (0°), stirred slurry of 950 mg of sodium hydride (60% dispersion in mineral oil) in 30 ml of dry THF, under argon, is added dropwise 2.3 ml of methyl acetoacetate. After 5 minutes, 13.5 ml of butyllithium (1.6M in hexanes) is added, and the mixture stirred another 5 minutes before addition of a solution of 3.51 g of the title compound of Preparation 83 (Formula U-3) in 4 ml of THF. The solution is stirred for 1 hour, then partitioned between ethyl acetate and cold dilute HCl. The aqueous phase is extracted with two additional portions of ethyl acetate, and the combined organic phase washed with brine and dried over magnesium sulfate. Removal of the solvent under reduced pressure

provides the intermediate ester with the following physical characteristics: TLC R_f 0.45 (50% ethyl acetate in hexane).

The ester is stirred in 20 ml of 1M sodium hydroxide, 80 ml of water, and 40 ml of methanol for 90 minutes, then the methanol is removed under reduced pressure. The aqueous phase is washed once with ether, the ether phase being discarded, and then acidified with dilute HCl. The resulting precipitate is extracted with four portions of dichloromethane, and the extract dried over magnesium sulfate and concentrated under reduced pressure. The residue is dissolved in 1:1 ether-hexane and the solution chilled to provide crystals, which are filtered, washed with ether-hexane, and dried under vacuum to afford 3.24 g of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ0.96, 1.4, 1.8, 2.0, 2.5, 2.7, 7.0, 7.1 ppm

IR 2962, 1655, 1604, 1510, 1221 cm^{-1}

M.P. 113°–114.5°

Anal. Found: C, 68.85; H, 6.99

MS: M+ 278

R_f 0.44 (5% methanol in dichloromethane)

PREPARATION 85

3-(1-(3-Benzyloxycarbonylaminophenyl)-2,2-dimethylpropyl)-5,6-dihydro-4-hydroxy-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-2-one (Formula U-6: R_1 is tert-butyl) Refer to Chart U

To a stirred solution of 3.06 g of the title compound of Preparation 84 (Formula U-4) and 2.81 of the title compound of Preparation 6 above (Formula B-2) in 30 ml of dry THF is added a solution of 2.93 g of $AlCl_3$ in 20 ml of THF. After two hours, 6.4 g of sodium carbonate decahydrate is added, and after five minutes the mixture is filtered through Celite with ether rinses. Removal of the solvent under reduced pressure provides the intermediate benzylidene compound of Formula U-5.

To this is added, under argon, 1.13 g of copper (I) bromide-dimethyl sulfide complex and 30 ml of THF, and the mixture is cooled to 0° for dropwise addition of 18.1 ml of tert-butylmagnesium chloride (1.0M in THF). After 10 minutes, the reaction is partitioned between ether and cold dilute HCl. The organic phase is washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel using 30–35% ethyl acetate in hexane affords 1.83 g of the title compound as a foam.

Physical characteristics are as follows:

^{1}H NMR δ0.87, 1.1, 1.3, 1.6–2.2, 2.5, 5.12, 6.8–7.6 ppm

HRMS: 574.2955

R_f 0.29 (35% ethyl acetate in hexane)

PREPARATION 86

3-(1-(3-Aminophenyl)-2,2-dimethylpropyl)-5,6-dihydro-4-hydroxy-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-2-one (Formula U-7: R_1 is tert-butyl) Refer to Chart U

A mixture of 1.83 g of the title compound of Preparation 85 (Formula U-6), 2.0 g of ammonium formate, and 400 mg of 10% palladium on carbon in 25 ml of methanol is stirred under argon for 90 minutes, then filtered through Celite. The solvent is removed under reduced pressure and the residue flash chromatographed on silica gel using 10% ethyl acetate in dichloromethane to provide 1.24 g of the title compound as a white foam.

Physical characteristics are as follows:

R_f 0.28 (10% ethyl acetate in dichloromethane)

The compound of Formula U-7 wherein R_1 is ethyl is prepared from U-4 by analogous procedures as in the preparation of U-7 wherein R_1 is tert-butyl (Preparations 85 and 86).

EXAMPLE 252

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula U-8: R_1 is tert-butyl, R_2 is 1-methylimidazole-4-yl) Refer to Chart U

To a cold (0°), stirred solution of 88 mg of the title compound of Preparation 86 (Formula U-7) and 32 μl of pyridine in 0.5 ml of dichloromethane is added 36 mg of 1-methylimidazole-4-sulfonyl chloride. After 90 minutes the reaction mixture is flash chromatographed on silica using 3–4% methanol in dichloromethane to provide 112 mg of the title compound as a white foam.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 0.96, 1.3, 1.7, 2.35, 2.5, 3.6, 3.7, 6.8–7.5 ppm

HRMS: 583.2525

R_f 0.31 (5% methanol in dichloromethane)

EXAMPLE 253

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula U-8: R_1 is tert-butyl, R_2 is 5-cyanopyridine-2-yl) Refer to Chart U

Using the general sulfonylation procedure of Example 252, 88 mg of the amine of Preparation 86 (Formula U-7, R_1 is tert-butyl) is reacted with 5-cyanopyridine-2-sulfonyl chloride. Flash chromatography on silica using 10–15% ethyl acetate in dichloromethane provides 107 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.92, 1.3, 1.7, 2.5, 6.8–7.5, 8.0, 8.9 ppm

HRMS: 606.2423

EXAMPLE 254

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula U-8: R_1 is ethyl, R_2 is 1-methylimidazole-4-yl) Refer to Chart U

Using the general sulfonylation procedure of Example 252, 82 mg of the amine of Formula U-7, wherein R_1 is ethyl, is reacted with 1-methylimidazole-4-sulfonyl chloride. Flash chromatography on silica using 3% methanol in dichloromethane provides 101 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.8, 1.3, 1.6–2.2, 2.5, 3.5, 3.6, 3.9, 6.8–7.4 ppm

HRMS: 555.2192

R_f 0.29 (5% methanol in dichloromethane)

EXAMPLE 255

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula U-8: R_1 is ethyl, R_2 is 5-cyanopyridine-2-yl) Refer to Chart U

Using the general sulfonylation procedure of Example 252, 82 mg of the amine of Formula U-7, wherein R_1 is ethyl, is reacted with 5-cyanopyridine-2-sulfonyl chloride. Flash chromatography on silica using 10–15% ethyl acetate in dichloromethane provides 101 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.9, 1.3, 1.6–2.2, 2.5, 3.9, 6.9–7.3, 8.0, 8.1, 8.9 ppm

HRMS: 557.2059

R_f 0.44 (20% ethyl acetate in dichloromethane)

PREPARATION 87

1,5-Bis-(4-fluorophenyl)-penta-1,4-dien-3-one (Formula V-2) Refer to Chart V

To a rapidly stirred, ambient temperature solution of 10 g of sodium hydroxide in 100 ml of water and 80 ml of ethanol is added a mixture of 12.4 g of 4-fluorobenzaldehyde of Formula V-1 and 2.9 g of acetone. After 45 minutes, the resulting precipitate is filtered off, washed well with water, and dried under vacuum. Recrystallization from ethyl acetate-hexane yields 10.7 g of the title compound as light yellow platelets.

Physical characteristics are as follows:

^{1}H NMR δ6.9–7.2, 7.6–7.7 ppm

IR 1653, 1587, 1508, 984, 835 cm^{-1}

MS: M+ 270

Anal. Found: C, 75.40; H, 4.41

R_f 0.35 (dichloromethane)

M.P. 152°–154°

PREPARATION 88

1,5-Bis-(4-fluorophenyl)-pentane-3-one (Formula V-3) Refer to Chart V

To a solution of 5.41 g of dienone of Preparation 87 (Formula V-2) in 10 ml of THF and 50 ml of methanol is added 2.0 g of magnesium chips. A water bath is used to maintain the temperature of the reaction near ambient. After the magnesium has been consumed, the reaction mixture is partitioned between dichloromethane and dilute HCl, with two additional dichloromethane extractions of the aqueous phase. The combined organic phase is dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography of the residue on silica using 50% dichloromethane in hexane affords 3.66 g of the title compound as a yellow oil.

Physical characteristics are as follows:

^{1}H NMR δ2.67, 2.85, 6.9, 7.1 ppm

IR 2932, 1716, 1603, 1511, 1223, 1159, 828 cm^{-1}

MS: M+ 274

R_f 0.28 (50% dichloromethane in hexane)

PREPARATION 89

4-Hydroxy-5,6-dihydro-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-2-one (Formula V-4) Refer to Chart V

Using the general acetoacetate condensation and ring closure procedure of Preparation 84 (Formula U-4), 3.9 g of the ketone of Preparation 88 (Formula V-3) is converted to 2.86 g of the title compound, which may be recrystallized from dichloromethane-hexane.

Physical characteristics are as follows:

^{1}H NMR δ2.1, 2.57, 2.7, 7.0, 7.1 ppm

IR 2924, 1659, 1578, 1508, 1241, 1216 cm^{-1}

MS: M+ 358

Anal. Found: C, 70.17; H, 5.50

M.P. 140°–141°

PREPARATION 90

3-[1-(3-Benzyloxycarbonylaminophenyl)-2,2-dimethylpropyl]-6,6-bis[2-(4-fluorophenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (Formula V-6: R_1 is tert-butyl) Refer to Chart V

Using the general benzylidene condensation and cuprate addition procedure of Preparation 85 (Formula U-6), 1.075 g of the dihydropyrone of Preparation 89 (Formula V-4) is converted to 707 mg of the title compound (via the intermediate compound of Formula V-5), which is purified by flash chromatography on silica gel using 40% ethyl acetate in hexane.

Physical characteristics are as follows:

^{1}H NMR δ1.07, 2.0, 2.6, 3.9, 5.16, 6.8–7.5 ppm

HRMS: 654.3023

R_f 0.25 (40% ethyl acetate in hexane)

PREPARATION 91

3-[1-(3-Aminophenyl)-2,2-dimethylpropyl]-6,6-bis[2-(4-fluorophenyl)ethyl]-4-hydroxy-5,6-dihydro-2H-pyran-2-one (Formula V-7: R_1 is tert-butyl) Refer to Chart V

Using the general transfer hydrogenolysis procedure of Preparation 86 (Formula U-7), 684 mg of the carbamate of Preparation 90 (Formula V-6, R_1 is tert-butyl) is converted to 497 mg of the title compound, which is purified by flash chromatography on silica gel using 5–10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ1.09, 2.0, 2.6, 6.8–7.1 ppm

R_f 0.34 (10% ethyl acetate in dichloromethane)

The compound of Formula V-7 wherein R_1 is ethyl is prepared from V-4 by analogous procedures as in the preparation of V-7 wherein R_1 is tert-butyl

(Preparations 90 and 91).

EXAMPLE 256

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula V-8: R_1 is tert-butyl, R_2 is 1-methylimidazole-4-yl) Refer to Chart V

Using the general sulfonylation procedure of Example 252, 78 mg of the amine of Preparation 91 (Formula V-7, R_1 is tert-butyl) is reacted with 1-methylimidazole-4-sulfonyl chloride. Flash chromatography on silica using 3–4% methanol in dichloromethane provides 92 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.94, 1.7–2.1, 2.5, 3.50, 6.8–7.4 ppm

HRMS: 664.2647

R_f 0.34 (5% methanol in dichloromethane)

EXAMPLE 257

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula V-8: R_1 is tert-butyl, R_2 is 5-cyanopyridine-2-yl) Refer to Chart V

Using the general sulfonylation procedure of Example 252, 78 mg of the amine of Preparation 91 (Formula V-7, R_1 is tert-butyl) is reacted with 5-cyanopyridine-2-sulfonyl chloride. Flash chromatography on silica using 10–15% ethyl acetate in dichloromethane provides 91.5 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.92, 1.9, 2.6, 3.2, 6.8–7.5, 8.0, 8.9 ppm

HRMS: 686.2488

R_f 0.28 (10% ethyl acetate in dichloromethane)

EXAMPLE 258

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula V-8: R_1 is ethyl, R_2 is 1-methylimidazole-4-yl) Refer to Chart V

Using the general sulfonylation procedure of Example 252, 74 mg of the amine of Formula V-7, wherein R_1 is ethyl, is reacted with 1-methylimidazole-4-sulfonyl chloride. Flash chromatography on silica using 3–4% methanol in dichloromethane provides 77 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.87, 2.0, 2.6, 3.62, 4.0, 4.05, 6.9–7.5 ppm

HRMS: 636.2350

R_f 0.31 (5% methanol in dichloromethane)

EXAMPLE 259

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula V-8: R_1 is ethyl, R_2 is 5-cyanopyridine-2-yl) Refer to Chart V

Using the general sulfonylation procedure of Example 252, 74 mg of the amine of Formula V-7, wherein R_1 is ethyl, is reacted with 5-cyanopyridine-2-sulfonyl chloride. Flash chromatography on silica using 10% ethyl acetate in dichloromethane provides 83 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.83, 2.0, 2.6, 3.96, 6.8–7.2, 8.0, 8.8 ppm

HRMS: 658.2200

R_f 0.49 (10% ethyl acetate in dichloromethane)

EXAMPLE 260

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 5-cyanopyridine-2-yl) Refer to Chart D

Using the general sulfonylation procedure of Example 252, 54 mg of the amine of Formula D-5 (R_1 and R_2 are propyl, R_3 is tert-butyl), prepared by procedures analogous to those described for the preparation of D-5 (where R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) in Preparation 20, is coupled with 5-cyanopyridine-2-sulfonyl chloride of Formula D-7 (R_4 is 5-cyanopyridine-2-yl) to yield, after flash chromatography on silica gel using 10–15% ethyl acetate in dichloromethane, 62 mg of the title compound as an amorphous solid.

Physical characteristics are as follows:

^{1}H NMR δ0.90, 1.2–1.8, 2.5, 7.0–7.4, 8.1, 8.2, 8.9 ppm

HRMS: 525.2305

R_f 0.44 (20% ethyl acetate in dichloromethane)

EXAMPLE 261

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 1-methylimidazole-4-yl) Refer to Chart D

Using the general sulfonylation procedure of Example 252, 54 mg of the amine of Formula D-5 (R_1 and R_2 are propyl, R_3 is tert-butyl), is coupled with 1-methylimidazole-4-sulfonyl chloride of Formula D-7 (R_4 is 1-methylimidazole-4-yl) to yield, after flash chromatography on silica gel using 3–5% methanol in dichloromethane, 53 mg of the title compound as an amorphous solid.

Physical characteristics are as follows:

^{1}H NMR δ0.9, 0.96, 1.2–1.8, 2.5, 3.6, 3.7, 6.9–7.5 ppm

MS: 503.2422

R_f 0.26 (5% methanol in dichloromethane)

EXAMPLE 262

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) Refer to Chart D

Using the general sulfonylation procedure of Example 252, 67 mg of the amine of Formula D-5 (R_1 and R_2 are propyl, R_3 is ethyl) of Preparation 20 is coupled with 5-cyanopyridine-2-sulfonyl chloride of Formula D-7 (R_4 is 5-cyanopyridine-2-yl) to yield, after flash chromatography on silica gel using 10% ethyl acetate in dichloromethane, 78 mg of the title compound as an amorphous solid.

Physical characteristics are as follows:

^{1}H NMR δ0.6–1.0, 1.2–1.8, 3.4, 3.5, 6.9–7.4, 8.0–8.2, 8.9 ppm

HRMS: 498.2072

R_f 0.38 (15% ethyl acetate in dichloromethane)

EXAMPLE 263

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) Refer to Chart D

Using the general sulfonylation procedure of Example 252, 79 mg of the amine of Formula D-5 (R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) of Preparation 20 is coupled with 5-cyanopyridine-2-sulfonyl chloride of Formula D-7 (R_4 is 5-cyanopyridine-2-yl) to yield, after flash chromatography on silica gel using 10% ethyl acetate in dichloromethane, 102 mg of the title compound as an amorphous solid.

Physical characteristics are as follows:

^{1}H NMR δ0.7–1.0, 1.2–2.6, 3.4, 3.5, 6.9–7.3, 7.9–8.2, 8.9 ppm

HRMS: 560.2231

R_f 0.37 (15% ethyl acetate in dichloromethane)

EXAMPLES 264–265

The following compounds are prepared using the general sulfonylation procedure of Example 246. The requisite amine is prepared analogously from the compound of Formula Q-1 (Preparation 69) following Preparations 80 and 81.

264) N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide

Physical characteristics are as follows:

^{1}H NMR δ0.0, 0.4, 0.6, 1.0, 1.2, 1.7, 2.5, 3.7, 4.1, 6.9–7.6

HRMS: 556.2833 (FAB)

265) N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran- 3-yl]-2,2-dimethyl-propyl)phenyl]-5-cyano-2-pyridinesulfonamide

Physical characteristics are as follows:

^{1}H NMR δ0.0, 0.4, 0.6, 1.0, 1.2, 1.7, 2.5, 4.1, 7.0–7.5, 8.0, 8.1, 9.0

HRMS: 578.2689 (FAB)

PREPARATION 92

(3(2E),4S)-3-(2-pentenyl)-4-phenyl-2-oxazolidinone (Formula W-4) Refer to Chart W

A 1 L round-bottomed flask with nitrogen inlet and addition funnel is charged with 6.92 g of (S)-(+)-4-phenyl-2-oxazolidinone and 250 mL of tetrahydrofuran and then cooled to −78° C. To the aforementioned solution is added 25.6 mL of n-butyl lithium during which time a white solid separated from the reaction solution, W-3. To that suspension is added 4.88 g of trans-2-pentenoyl chloride of formula W-2 (prepared from the treatment of commercially available trans-2-pentenoyl acid of formula W-1 with oxalyl chloride) in a small volume of THF. The resulting pale yellow homogeneous solution is allowed to warm to room temperature and stirred for another 20 min. The reaction mixture is quenched by the addition of saturated ammonium chloride solution and is extracted with ethyl acetate. The organic layer is separated, washed with brine and water, dried over magnesium sulfate, filtered and concentrated to give a white solid. Recrystallization from hot hexane gives 9.13 g of the title compound.

Physical characteristics are as follows:

MP 86°–88° C.

^{1}H NMR ($CDCl_3$) δ7.42–7.23, 7.18–7.09, 5.49, 4.70, 4.28, 2.28, 1.08 ppm.

$[\alpha]_D(CHCl_3)$=+109

Anal. found: C, 68.59; H, 6.25; N, 5.70

PREPARATION 93

(3(3R),4S)-3-[3-(3-Aminophenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula W-5) Refer to Chart W

A 1 L three-necked, round-bottomed flask with nitrogen inlet and addition funnel is charged with 8.90 g of copper(I) bromide-dimethyl sulfide complex and 125 mL of THF and then cooled to −40° C. To that suspension is added 43 mL of a 1M solution (in THF) of 3-[bis(trimethylsilyl)amino] phenylmagnesium chloride dropwise over 15 minutes. The reaction mixture is warmed 0° C. for 30 minutes and then a 25 mL THF solution containing 8.85 g of (3(2E),4S)-3-(2-pentenoyl)-4-phenyl-2-oxazolidinone of Preparation 92 (formula W-4) is added. The reaction mixture is stirred for 30 minutes at 0° C. and quenched by the addition of 1N HCl and then the pH readjusted with 1N NaOH to pH 8. The reaction is washed with water, brine and the organic is dried (Na_2SO_4). The organic solvent is evaporated in vacuo and the resulting oil chromatographed over 600 g of silica gel, eluting with ethyl acetate/hexane to afford 7.91 g of the title product.

Physical characteristics are as follows:

MP 94°–95° C.

^{1}H NMR ($CDCl_3$) δ7.28–7.25, 7.07–6.99, 6.60–6.51, 5.38, 4.63, 4.16, 3.52–3.44, 3.10–2.92, 1.65–1.53, 0.76 ppm.

IR (mineral oil) 3437, 3355, 1773, 1696, 1605, 1337, 1322, 1299, 1263, 1212, 1096, 1070, 791, 762, 704 cm^{-1}.

Anal. found: C, 71.00; H, 6.67; N, 8.17

EI-MS: [M+]=338.

$[\alpha]_D$ (19.87 mg/2 mL $CHCl_3$)=+60°

PREPARATION 94

3-[3-(3-[Bis(phenylmethyl)amino]phenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone, (3R)(4S) (Formula W-6) Refer to Chart W

To a mixture of 25 mL of Na_2CO_3 and 80 mL of methylene chloride was added 7.90 g of (3(3R),4S)-3-[3-(3-aminophenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone of Preparation 93 (formula W-5) followed by 15.94 g of benzyl bromide. That mixture is heated at 65° C. for 18 hours, the methylene chloride layer separated, dried (Na_2SO_4) and solvent evaporated to yield the crude product as a dark viscous oil. That oil is chromatographed over 700 g of silica gel eluding with 25% ethyl acetate/hexane to yield 8.55 g of the title compound.

Physical characteristics are as follows:

MP 92°–3° C.

^{1}H NMR ($CDCl_3$) δ7.24, 7.02, 6.53, 5.34, 4.59, 4.14, 3.44, 3.07, 2.89, 1.50, 0.64 ppm

Anal. found: C, 78.47; H, 6.68; N, 5.26

$[\alpha]_D$ (19.602 mg/2 mL $CHCl_3$)=+32°

PREPARATION 95

(3R)(4S) 3-[3-(3-[bis(phenylmethyl)amino]phenyl)-2-(2-methyl-1,3-dioxolan-2-yl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula W-8) Refer to Chart W

To 25 mL of methylene chloride is added 2.1 g of the amide of formula W-6 of Preparation 94 and the resulting solution cooled to −78° C. under an atmosphere of nitrogen. To that solution is added 872 μL of neat $TiCl_4$ followed by the addition of 732 μL of diisopropylethylamine. The resulting mixture is warmed to 0° C. for 30 minutes and then cooled back to −78° C. and 1.3 g of 2-methoxy-2-methyl-1,3-dioxolane of formula W-7 and the resulting reaction is warmed to 0° C. and stirred for 1 hour, then quenched with saturated ammonium chloride and extracted with methylene chloride. The organic extract is dried (Na_2SO_4) and solvent removed in vacuo to afford the crude material. Silica gel chromatography using 100 g of support and eluding with 10% hexane/methylene chloride afforded 1.76 g of the title product.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.36, 7.08, 5.99, 5.42, 4.80, 4.68, 4.60, 4.25, 3.68, 3.57, 3.48, 3.07, 2.90, 1.5, 0.86, 0.54 ppm

Anal. found: C, 75.34; H, 6.99; N, 4.87

$[\alpha]_D$ (18.086 mg/2 mL $CHCl_3$)=+25°

PREPARATION 96

(3R)(4S)-3-[2-acetyl-3-[3-(bis(phenylmethyl)amino) phenyl]-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula W-9) Refer to Chart W

To 25 mL of tetrahydrofuran and 10 mL of 30% $HClO_4$ is added 5.0 g of the title compound of Preparation 95 (formula W-8) and the resulting solution stirred at 40° C. for 3 hours. The reaction is neutralized with saturated $NaHCO_3$ to pH 8 and then extracted with 400 mL of ether. The ether layer is washed with water, brine and then dried (Na_2SO_4) and solvent evaporated in vacuo to afford an oil. Chromatography over 300 g of silica gel eluting with 15% acetone/hexane afforded 4.12 g of the title compound.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.31, 7.08, 6.59, 6.55, 5.42, 4.67, 4.61, 4.22, 3.09, 1.63, 1.56, 0.61 ppm

Anal. found: C, 77.11; H, 6.76; N, 4.98

$[\alpha]_D$ (20.172 mg/2 mL $CHCl_3$)=−10°

PREPARATION 97

(3R)(4S) 3-[2-[1-(3-[bis(phenylmethyl)amino]phenyl) propyl]-5-hydroxy-1,3-dioxo-5-propyloctyl]-4-phenyl-2-oxazolidinone (Formula W-10) Refer to Chart W

To 25 mL of methylene chloride is added 1.32 g of the compound of Preparation 96 (formula W-9) and the resulting solution cooled to −78° C. under an atmosphere of nitrogen. To that solution is added 279 μL of $TiCl_4$ and 450 μL of diisopropylethylamine and stirring continued for 1 hour. To this solution is added 689 μL of heptanone and the reaction temperature raised to 0° C. for 1.5 hours. The reaction is then quenched by the addition of a saturated ammonium chloride solution and the mixture extracted with methylene chloride. The organic extract is washed with saturated $NaHCO_3$, dried (Na_2SO_4) and evaporated in vacuo to yield the crude product. Chromatography over 100 g of silica gel eluting with 5% hexane/methylene chloride affords 1.16 g of the title compound as an off white foam.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) 7.36, 7.07, 6.58, 6.54, 5.44, 5.24, 4.69, 4.61, 4.27, 3.21, 3.01, 2.48, 1.90, 1.54, 1.15, 0.81, 0.76, 0.58 ppm

Anal. found: C, 76.62; H, 7.63; N, 4.17 $[\alpha]_D$ (15.380 mg/2 mL $CHCl_3$)=+16°

PREPARATION 98

(3S)-3-[1-(3-(Bis(phenylmethyl)amino)phenyl)propyl]-6,6-dipropyl-5,6-dihydro-4-hydroxy-2H-pyran-2-one (Formula W-11) Refer to Chart W

To 10 mL of dry tetrahydrofuran is added 770 mg of the title compound of Preparation 97 (formula W-10) and the resulting solution cooled to 0° C. under an atmosphere of nitrogen. To that solution is added 150 mg of a 60% oil dispersion of sodium hydride and the reaction is warmed to

20° C. and stirring continued for 16 hours. The reaction is quenched with saturated ammonium chloride and extracted with ethyl acetate. The extract is dried and evaporated in vacuo to yield the crude product. Chromatography over 100 g of silica gel eluting with 15% EtOAc/hexane affords 560 mg of the title product.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) 7.34, 6.69, 5.87, 4.69, 4.60, 4.09, 2.28, 2.17, 1.89, 1.73, 1.55, 1.32, 0.88 ppm

[Anal. found: C, 79.71; H, 8.07; N, 2.61]

[$[\alpha]_D$ (15.998 mg/2 mL $CHCl_3$)=−56°]

PREPARATION 99

(3S)-3-[1-(3-aminophenyl)propyl]-6,6-dipropyl-5,6-dihydro-4-hydroxy-2H-pyran-2-one (Formula W-12) Refer to Chart W

The title compound of Preparation 98 (formula W-11) ((3R)-3-[1-(3-bis-benzylaminophenyl)propyl]-6,6-bispropyl-5,6-dihydro-4-hydroxypyran-2-one) 110 mg is added to 20 mL of ethyl acetate. To that solution is added 50 mg of 10% Pd/C and the resulting mixture is hydrogenated at 50 psi for 6 hours. The reaction is filtered through celite to yield 83 mg of the title product.

Physical characteristics are as follows:

IR 2957, 2922, 2855, 2871, 2854, 1378, 1605, 1459, 1617, 1262, 1319, 1251, 1282, 1107 cm^{-1}.

$[\alpha]_D$ (6.526 mg/2 mL CH_3OH)=−34°

PREPARATION 100

(4R)3-(1-oxo-2-pentenyl)-4-phenyl-2-oxazolidinone (Formula X-4) Refer to Chart X

A 2-L, three-necked, round-bottomed flask with nitrogen inlet and addition funnel is charged with (R)-(−)-4-phenyl-2-oxazolidinone (31.2 g) and tetrahydrofuran (1.2 L) and cooled to −78° C. The addition funnel is charged with n-butyllithium (1.6M in hexanes, 117 mL), which is added dropwise to the reaction mixture over 20 min. A white precipitate is formed which is X-3. The reaction mixture is stirred for an additional 30 min at −78° C. The addition funnel is then charged with trans-2-pentenoyl chloride of formula X-2, prepared from the acid of formula X-1, (24.4 g) and tetrahydrofuran (50 mL), and this solution is added to the reaction mixture dropwise over 10 min. The resulting pale yellow homogeneous solution is allowed to warm to room temperature and is stirred for another 30 min. The reaction mixture is quenched by the addition of saturated ammonium chloride solution and is extracted with ethyl acetate (2500 mL). The organic layer is separated, washed with brine and water, dried over magnesium sulfate, filtered and concentrated to give 48 g of a white solid. The solid is recrystallized from ethyl acetate (100 mL) and hexane (200 mL) to give 38.0 g the title product as a white solid.

Physical characteristics are as follows:

MP 86°–88° C.

^{1}H NMR ($CDCl_3$) δ7.42–7.23, 7.18–7.09, 5.49, 4.70, 4.28, 2.28, 1.08 ppm.

IR (mineral oil) 1785, 1764, 1686, 1638, 1349, 1336, 1329, 1257, 1234, 1214, 1087, 1076, 756, 716, 699 cm^{-1}

EI-MS: [M+]=245.

PREPARATION 101

(3(3S),4R)-3-[3-(3-aminophenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula X-5) Refer to Chart X

A 2-L, three-necked, round-bottomed flask with nitrogen inlet and addition funnel is charged with copper(I) bromide-dimethyl sulfide complex (25.1 g) and tetrahydrofuran (250 mL) and cooled to −40° C. The addition funnel is charged with 3-[bis(trimethylsilyl)amino]phenylmagnesium chloride (1.0M in THF, 122 mL), which is added dropwise to the reaction mixture over 20 min. The reaction mixture is then allowed to warm from −40° C. to −20° C. over 20 min. The addition funnel is charged with 25 g of the title compound of Preparation 100 (formula X-4) and tetrahydrofuran (100 mL), and this solution is added to the reaction mixture dropwise over 30 min at 0° C. The reaction mixture is then stirred for 15 min at 0° C. and quenched by the addition of saturated ammonium chloride solution (adjusted to pH 8 by addition of ammonium hydroxide). The reaction mixture is poured into ether (2 L) and washed with the ammonium chloride solution until the aqueous layer is no longer blue in color. The organic layer is separated, washed with water, dried over magnesium sulfate, filtered and concentrated to give 58 g of a yellow oil. The crude reaction mixture is then stirred at room temperature in a slurry of silica gel (75 g) and methylene chloride (100 mL) for 1 h. The mixture is filtered, washed with methanol, and concentrated to give 49 g of an oil. Column chromatography on 300 g silica (eluting with 10–75% ethyl acetate-hexane, 100% ethyl acetate) yields 30.9 g of a yellow oil. The oil is crystallized from ethyl acetate (75 mL) and hexane (150 mL) to give 21.4 g of the title compound as a white solid.

Physical characteristics are as follows:

MP 94°–97° C.

^{1}H NMR ($CDCl_3$) δ7.28–7.25, 7.07–6.99, 6.60–6.51, 5.38, 4.63, 4.16, 3.52–3.44, 3.10–2.92, 1.65–1.53, 0.76 ppm.

IR (mineral oil) 3437, 3355, 1773, 1696, 1605, 1337, 1322, 1299, 1263, 1212,1096, 1070, 791, 762, 704 cm^{-1}.

EI-MS: [M+]=338.

PREPARATION 102

(3(3S),4R)-3-[3-(3-(phenylmethyl)amino)phenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula X-6) Refer to Chart X

To a mixture of 80 mL of Na_2CO_3 and 280 mL of methylene chloride is added 21.0 g of (3(3S),4R)-3-[3-(3-aminophenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (formula X-5) of Preparation 101 followed by 23.4 g of benzyl bromide. That mixture is heated at 65° C. for 18 hours, the methylene chloride layer separated, dried (Na_2SO_4) and solvent evaporated to yield the crude product as a dark viscous oil. The oil is chromatographed over 700 g of silica gel eluding with 25% ethyl acetate/hexane to yield 31.42 g of the title compound.

Physical characteristics are as follows:

MP 91.8–93.5

^{1}H NMR ($CDCl_3$) δ7.32, 7.08, 6.60, 5.34, 4.67, 4.15, 3.43, 3.02, 2.91, 1.56, 0.65 ppm

PREPARATION 103

(3S)(4S)-3-[3-[3-(Bis(phenylmethyl)amino]phenyl]-2-(2-methyl-1,3-dioxolan-2-yl]-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula X-8) Refer to Chart X

To 12 mL of methylene chloride, under nitrogen, is added 1.55 grams of (3(3S),4R)-3-[3-(3-bisbenzylaminophenyl) pentanoyl]-4-phenyl-2-oxazolidinone (formula X-6) of Preparation 102 and the resulting solution cooled to −78° C. To the aforementioned solution is added 646 μl of $TiCl_4$ followed by the addition of 525 μl of diisopropylethylamine. After stirring at 0° C. for 30 minutes the reaction is cooled back to −78° C. and 886 μl of 2-methoxy-2-methyl-1,3-dioxolane (formula X-7) (also W-7) is added. The reaction is stirred for 1 hour and then quenched by the addition of saturated NH_4Cl, then saturated $NaHCO_3$ (pH 8) and finally extraction of the aqueous with both methylene chloride and ethyl ether. Evaporation of solvent affords a viscous oil which is chromatographed over 150 g of silica gel eluting

with 7% hexane/methylene chloride to afford 1.14 g of the title compound.

Physical characteristics are as follows:

IR (mineral oil) 2920, 2954, 2854, 2870, 1776, 1376, 1453, 1196, 699 cm^{-1}.

Anal. found: C, 75.27; H, 6.68; N, 4.55

PREPARATION 104

(3S)(4R) 3-[2-Acetyl-3-[3-[bis(phenylmethyl)amino] phenyl]-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula X-9) Refer to Chart X

To 15 mL of THF is added 960 mg of (3(3S),4R)-3-[2-(2-methyl-1,3-dioxan-2-yl)-3-(3-bisbenzylaminophenyl) pentanoyl]-4-phenyl-2-oxazolidinone (formula X-8) of Preparation 103. To that solution is then added 4 mL of 30% perchloric acid and the resulting mixture stirred at 40° C. for 2 hours. The reaction is cooled to room temperature and quenced with the addition of excess saturated $NaHCO_3$. The reaction is extracted with 200 mL of ethyl ether, dried (Na_2SO_4) and solvent removed in vacuo to yield 981 mg of the crude product. Chromatography over 100 g of silica gel eluding with 10% pentane/methylene chloride affords 854 mg of the title compound.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ7.40, 7.08, 6.61, 6.56, 5.41, 4.96, 4.66, 4.61, 4.21, 3.09, 1.63, 1.65, 0.61

IR (mineral oil) 1778, 1718, 1600, 1695, 1452, 1335, 1385, 1200 cm^{-1}.

EI-MS: [M+]=560.

Anal. found: C, 76.81; H, 6.59; N, 4.84.

PREPARATION 105

(3S)(4R) 3-[2-[1-[3-[bis(phenylmethyl)amino]phenyl]-propyl]-5-hydroxy-1,3-dioxo-5-propyloctyl]-4-phenyl-2-oxazolidinone (Formula X-10) Refer to Chart X

To 8 mL of methylene chloride under nitrogen is added 440 mg of (3(3S),4R)- 3-[2-(acetyl)-3-(3-bisbenzylaminophenyl)pentanoyl]-4-phenyl-2-oxazolidinone (formula X-9) of Preparation 104 and that solution is cooled to −78° C. To that solution is added 90 μl of $TiCl_4$ followed by the addition of 143 μl of diisopropylethylamine. That solution is warmed to 0° C. for 40 minutes and then cooled back to −78° C. at which time 126 μl of 4-heptanone is added and the reaction temperature is elevated to 0° C. and stirring continued for 1.5 hours. The reaction is quenced with the addition of saturated NH_4Cl followed by the addition of saturated $NaHCO_3$. The reaction is extracted with methlene chloride (3×60 mL), dried (Na_2SO_4) and evaporated in vacuo to yield the crude product as an oil. That material is chromatographed over silica gel (100 g) eluting with 10% pentane/methylene chloride to afford 293 mg of the title compound.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ7.28, 7.07, 6.56, 5.44, 5.24, 4.68, 4.61, 4.26, 3.21, 3.10, 2.48, 1.90, 1.55, 1.21, 0.81, 0.74, 0.58

IR (mineral oil) 2959, 2931, 1779, 1720, 1690, 1600, 1494, 1452, 1385, 1359, 1334, 1238, 698 cm^{-1}.

PREPARATION 106

(3R) 3-[1-[3-[bis(phenylmethyl)amino]phenyl]propyl]-5,6-dihydro-4-hydroxy-6,6-dipropyl-2H-pyran-2-one (Formula X-11) Refer to Chart X

To 3 mL of THF was added 28 mg of NaH under nitrogen. To that suspension is added 418 mg of (3(3S),4R)-3-[2-((3-hydroxy-3-propyl)hexanoyl)-3-(3-bisbenzylaminophenyl) pentanoyl]-4-phenyl-2-oxazolidinone (Formula X-10) of Preparation 105 also in 3 mL of THF at 20° C. The reaction is stirred for 16 hours, cooled to 0° C. and quenched by addition of 1N HCl. The reaction is then made basic with the addition of saturated $NaHCO_3$. The aqueous is extracted several times with ethyl acetate, the organic extracts dried (Na_2SO_4) and solvent is removed in vacuo to yield 518 mg of crude product. Chromatography over silica gel eluting with 15% EtOAc/hexane affords 128 mg of the title compound.

Physical characteristics are as follows:

IR (mineral oil) 2959, 2931, 2873, 1636, 1599, 1451, 1465, 1386, 1363, 1328, 1249, 1260, 696 cm^{-1}.

EI-MS: [M+]=511.

PREPARATION 107

(3R) 3-[1-[3-[amino]phenyl]propyl]-5,6-dihydro-4-hydroxy-6,6-dipropyl-2H-pyran-2-one (Formula X-12) Refer to Chart X

The dihydropyrone of formula X-11 ((3R)-3-[1-(3-bisbenzylaminophenyl)-propyl]-6,6-bispropyl-5,6-dihydro-4-hydroxypyran-2-one) of Preparation 106, 110 mg, is added to 20 mL of ethyl acetate. To that solution is added 50 mg of 10% Pd/C and the resulting mixture is hydrogenated at 50 psi for 6 hours. The reaction is filtered through celite to yield 83 mg of the title product.

Physical characteristics are as follows:

IR (mineral oil) 2961, 2932, 2873, 1682, 1623, 1604, 1458, 1384, 1369, 1319, 1282, 1259, 1150, 1108 cm^{-1}.

EI-MS: [M+]=331

PREPARATION 108

2-Phenethyl-2-propen-1-ol (Formula BB-2) Refer to Chart BB

To a cooled (−10° C.) solution of N,N,N,N,-tetramethyl-1,2-ethylenediamine (24.1 mL) in hexane (50 mL) is slowly added butyl lithium (100 mL of a 1.6M solution in hexane). After stirring for 45 minutes at −10° C. the mixture is cooled (−78° C.) and 2-methyl-2-propen-1-ol (BB-1, 6.41 mL) is added dropwise. The reaction is allowed to warm to room temperature and stirred an additional 72 h. The mixture is cooled to −78° C. and a solution of benzyl bromide (8.6 mL) in anhydrous THF (10 mL) is added slowly. The mixture is stirred at −78° C. for 1 hour then gradually allowed to warm to room temperature. After stirring an additional 2 hours, the reaction is quenched by the addition of saturated aqueous NH_4Cl. The organic layer is diluted with diethyl ether and washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography using methylene chloride/ethyl acetate/hexane (1:1:6) as eluent affords the title compound (3.5 g) as an oil.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ7.31–7.16, 5.07, 4.93, 4.09, 2.82–2.76, 2.41–2.36 ppm.

^{13}C NMR ($CDCl_3$) δ148.30, 141.69, 128.24, 125.80, 109.76, 65.90, 34.52, 34.16 ppm.

PREPARATION 109

(2S)-2-Phenethyloxiranemethanol (Formula BB-8) Refer to Chart BB

To a cooled (−20° C.) slurry of molecular sieves (4 Å, crushed and freshly activated, 150 mg) in methylene chloride (1.5 mL) is added diethyl L-tartrate (22 mg) and titanium(IV) isopropoxide (25 mg). The mixture is stirred for 30 min at −20° C. and tert-butyl hydroperoxide (0.84 mL of a 5–6M solution in nonane) is added. After an additional 25 min at −20° C., a solution of allylic alcohol of formula BB-2 (300 mg) of Preparation 108 in methylene chloride (0.5 mL) is slowly added. The mixture is stirred overnight at −20° C. then warmed to −10° C. After an additional 4 hours the reaction is warmed to 0°–5° C. and quenched with the

addition of water (1 mL). After warming to room temperature, stirring is continued for 1 hour and tartrates hydrolysed by the addition of a 30% aqueous NaOH solution saturated with NaCl (0.1 mL). After 30 minutes, the mixture is filtered through Celite and the aqueous phase extracted with several portions of methylene chloride. The combined organic layers are dried ($MgSO_4$), filtered and concentrated in vacuo to provide a residue which is purified by flash chromatography using hexane and a gradient of ethyl acetate (10–20%) as eluent to afford the title product of formula BB-3 (223 mg) as an oil. The enantiomeric excess of the reaction is determined to be 86% by analysis of the ^1H NMR (C_6D_6) of the Mosher ester formed by the reaction of BB-3 with (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (J. A. Dale, D. L. Dull, H. S. Mosher, J. Org. Chem. (1969) 34:2543).

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ7.34–7.16, 3.83–3.61, 2.89–2.87, 2.72–2.64, 2.17–2.04, 1.89–1.79 ppm

^{13}C NMR ($CDCl_3$) δ141.17, 137.58, 128.49, 128.21, 126.11, 63.00 59.57, 49.92, 33.58, 30.82 ppm.

PREPARATION 110

(2S)-2-Phenethyl-2-phenylmethoxymethyloxirane (Formula BB-9) Refer to Chart BB

To a cooled (0°–5° C.) slurry of sodium hydride (124 mg of a 60% suspension in mineral oil) in THF (10 mL) is added alcohol of formula BB-3 (460 mg) of Preparation 109. The mixture is stirred at 0°–5° C. for 5 minutes, allowed to warm to room temperature and stirred an additional 30 minutes. Benzyl bromide (441 mg) is added and the mixture stirred at room temperature overnight. The mixture is quenched with brine (10 mL) and diluted with ethyl ether. The organic layer is washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a residue which is purified by flash chromatography using hexane and a gradient of ethyl acetate (2–5%) as eluent to afford the title product (510 mg) as an oil.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ7.34–7.13, 4.59–4.49, 3.64–3.45, 2.75–2.59, 2.19–2.09, 1.94–1.84

^{13}C NMR ($CDCl_3$) δ141.42, 137.93, 128.58, 128.38, 127.88, 125.94, 73.23, 71.98, 58.21, 50.37, 33.65, 30.83 ppm.

PREPARATION 110a

(3S)-1-Phenyl-3-(phenylmethoxymethyl) hexan-3-ol (Formula BB-10) Refer to Chart BB

To a cooled (−45° C.) solution of Li_2CuCl_4 (0.28 mL of a 0.1M solution in THF) in THF (2 mL) is added ethylmagnesium bromide (0.203 mL of a 3M solution in ethyl ether). The brown solution is stirred at −45° C. for 45 minutes and the epoxide of formula BB-4 (150 mg) of Preparation 110 is added dropwise over ca. 10 minutes. After one hour the reaction is quenched by the addition of saturated aqueous NH_4Cl and the aqueous layer extracted with ethyl acetate. The combined organic layers are washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a residue which is purified by flash chromatography using hexane/ethyl acetate (5%) as eluent to afford the title product (150 mg) as an oil.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ7.38–7.14, 4.54, 3.37, 2.66–2.58, 2.20, 1.88–1.76, 1.58–1.52, 1.39–1.25, 0.92

^{13}C NMR ($CDCl_3$) δ142.61, 138.10, 128.41, 128.33, 127.71, 127.63, 125.68, 75.45, 73.79, 73.44, 38.95, 38.52, 29.86, 16.79, 14.37 ppm.

PREPARATION 110b

(2R)-2-Phenethyl-2-(p-toluenesulfonyloxymethyl) oxirane (Formula BB-13) Refer to Chart BB

To a cooled (ca. −10° C.) solution of the compound of formula BB-8 (245 mg) of Preparation 109 in methylene chloride (4 mL) is added 4-toluenesulfonyl chloride (302 mg), triethylamine (160 mg) and 4-dimethylaminopyridine (8 mg). The mixture is stirred at ca. −10° C. overnight then warmed to 0°–5° C. for 1 hour. The mixture is diluted with methylene chloride, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a residue which is purified by flash chromatography using hexane/ ethyl acetate (5%) as eluent to afford the title compound (448 mg).

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ7.79, 7.33, 7.28–7.08, 4.13–3.98, 2.64–2.58, 2.44, 2.11–2.00, 1.92–1.82

^{13}C NMR ($CDCl_3$) δ145.17, 140.67, 132.53, 129.96, 128.48, 128.19, 127.95, 126.15, 71.98, 56.49, 50.63, 32.89, 30.37, 21.64 ppm.

PREPARATION 110c

(2S)-2-Phenethyl-2-propyl oxirane (Formula BB-12) Refer to Chart BB

To a cooled (−45° C.) solution of Li_2CuCl_4 (0.3 mL of a 0.1M solution in THF) in THF (2 mL) is added ethylmagnesium bromide (0.22 mL of a 3M solution in ethyl ether). The brown solution is stirred at −45° C. for 45 minutes, cooled to −65° C. then tosylate of formula BB-13 (200 mg) of Preparation 110b is added dropwise over ca. 10 minutes. The mixture is stirred for 2.5 hours, warmed to −50° C. for 2 hours and then quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer is extracted with ethyl acetate and the combined organic layers washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a residue which is purified by flash chromatography using hexane/ethyl acetate (5%) as eluent to afford the title product (60 mg) and hydroxytosylate of formula BB-14 (47 mg).

Hydroxytosylate of formula BB-14 is converted to the epoxide of formula BB-12 as follows: To a cooled (0°–5° C.) solution of the compound of formula BB-14 (43 mg) in methanol (2 mL) is added anhydrous K_2CO_3 (20 mg). After 1 hour at 0°–5° C. the mixture is warmed to room temperature, stirred an additional 90 minutes then quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer is extracted with ethyl acetate and the combined organic layers washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to provide a residue which is purified by flash chromatography using hexane/ethyl acetate (5%) to afford the epoxide of formula BB-12 (20 mg).

Physical characteristics for BB-12 are as follows:

^1H NMR ($CDCl_3$) δ7.31–7.16, 2.68, 2.59, 1.98–1.82, 1.73–1.37, 0.94

^{13}C NMR ($CDCl_3$) δ141.71, 128.41, 128.24, 125.92, 59.11, 52.57, 36.42, 36.02, 31.03, 18.19, 14.22 ppm.

Physical characteristics for BB-14 are as follows:

^1H NMR ($CDCl_3$) δ7.79, 7.34, 7.29–7.11, 3.90, 2.58–2.53, 2.44, 1.87, 1.77–1.72, 1.54–1.48, 1.31–1.21, 0.89

^{13}C NMR ($CDCl_3$) δ145.10, 141.66, 132.50, 129.97, 128.45, 128.25, 127.97, 125.96, 74.33, 73.07, 38.37, 37.87, 29.37, 21.66, 16.47, 14.48 ppm.

PREPARATION 111

(4S)-3-acetyl-4-phenyl-2-oxazolidinone (Formula FF-3) Refer to Chart FF

To a solution of (S)-(+)-4-phenyl-2-oxazolidinone of formula FF-2 (20 g) in anhydrous tetrahydrofuran (600 mL), cooled to −78° C. is added a solution of 1.6M n-butyllithium in hexanes (77.8 mL) and the resulting suspension stirred at −78° C. for 30 minutes. The suspension is treated with acetyl

chloride of formula FF-1 (10.23 mL) and then gradually allowed to warm to room temperature. The reaction mixture is quenched with 1 L of saturated ammonium chloride and then partitioned between water and ethyl acetate. The organic layer is separated and the aqueous layer reextracted twice with ethyl acetate. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude solid is recrystallized from ethyl acetate/hexane affording (21.27 g,) as a white solid.

Physical Characteristics are as follows:

Mp 86°–87° C.

^{1}H NMR ($CDCl_3$) δ7.42–7.26, 5.44–5.40, 4.68, 4.30–4.26, 2.52 ppm

^{13}C NMR ($CDCl_3$) δ169.50, 153.71, 138.81, 128.97, 128.53, 125.73, 69.73, 57.20, 23.59 ppm

PREPARATION 112

(3(2E),4S)-3-[4,4-dimethyl (2-pentenoyl)]-4-phenyl-2-oxazolidinone (Formula FF-4) Refer to Chart FF

To a solution of the compound of formula FF-3 of Preparation 111 (21.27 g) in anhydrous methylene chloride (500 mL), cooled to −78° C., is added titanium tetrachloride (12.0 mL) in a dropwise manner. The suspension is treated with diisopropylethylamine (19.9 mL) and is allowed to stir at −78° C. for 30 minutes. The suspension is then treated with trimethylacetaldehyde (11.4 mL) followed by diisopropylethylamine (19.9 mL) and allowed to gradually warm to room temperature. After 1 hour the reaction mixture is quenched with water (200 mL) and stirred vigorously for 15 minutes. The organic layer is separated and the aqueous layer is reextracted with methylene chloride. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude solid is recrystallized from ethyl acetate/hexane affording 21.6 grams of the title compound as a off-white solid:

Physical characteristics are as follows:

Mp 148°–149° C.

^{1}H NMR ($CDCl_3$) δ7.42–7.05 , 5.51–5.46, 4.69, 4.30–4.25, 1.09 ppm

^{13}C NMR ($CDCl_3$) δ165.17, 161.61, 153.70, 139.16, 129.12, 128.61, 125.97, 115.71, 69.88, 57.74, 34.31, 28.56 ppm;

PREPARATION 113

(3(3S),4S)-3-[3-(3-Aminophenyl)-4,4-dimethylpentanoyl]-4-phenyl-2-oxazolidinone (Formula FF-5) Refer to Chart FF

To a slurry of copper(I) bromide dimethylsulfide complex (18.76 g) in anhydrous tetrahydrofuran (60 mL), cooled to −78° C., is added a 1.0M solution of 3-[bis(trimethylsilyl) amino]phenylmagnesium chloride in tetrahydrofuran (182.2 mL) and the resulting slurry stirred at −78° C. for 5 minutes. The slurry is allowed to warm to −15° C. for 15 minutes and then cooled to −78° C. The slurry is then treated with the compound of formula FF-4 of Preparation 112 (16.6 g) added via a solid addition funnel and allowed to stir at −78° C. for 3 hours. The reaction mixture is poured into saturated ammonium chloride (200 mL) and then partitioned between water and ethyl acetate. The organic layer is separated and the aqueous layer (pH 8) is basified to pH 9.5 with concentrated ammonium hydroxide. The aqueous layer is reextracted three times with ethyl acetate, the combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude residue is slurried in chloroform (400 mL) and 200 g of silica gel (230–400 mesh) at room temperature for 2 hours. The slurry is filtered and the solids washed several times with chloroform followed by methanol. The filtrate is concentrated in vacuo. Purification by flash chromatography eluting with hexane/ethyl acetate (15–40%) afford 17.52 grams of the title compound as a light yellow solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.26–7.12, 7.01, 6.74–6.70, 6.61–6.50, 5.32–5.28, 4.56, 4.11–3.95, 3.48, 2.97–2.91, 0.91 ppm

^{13}C NMR ($CDCl_3$) δ172.34, 153.51, 145.37, 142.24, 138.12, 128.67, 128.23, 127.68, 124.71, 119.80, 116.49, 113.02, 69.39, 57.39, 52.30, 34.75, 33.49, 27.83 ppm

PREPARATION 114

(3(3S),4S)-3-[3-(3-Bisbenzylaminophenyl)-4,4-dimethylpentanoyl]-4-phenyl-2-oxazolidinone (Formula FF-6) Refer to Chart FF-6

To a solution of the compound of formula FF-5 of Preparation 113 (15.0 g) in methylene chloride (190 mL) at room temperature is added saturated sodium carbonate (48.7 mL) followed by benzyl bromide (14.3 mL) and the resulting mixture is refluxed for 24 hours. The reaction mixture is allowed to cool to room temperature and partitioned between water (300 mL) and methylene chloride. The organic layer is separated, washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification by flash chromatography eluting with hexane/ethyl acetate (10–25%) affords 15.1 grams of the title compound as a white solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.29–6.99, 6.69–6.49, 5.32–5.26, 4.71–4.50, 4.06–3.94, 2.90–2.81, 0.73 ppm

^{13}C NMR ($CDCl_3$) δ172.79, 153.78, 148.32, 142.08, 139.04, 138.48, 129.07, 128.59, 128.37, 127.89, 126.83, 124.92, 118.44, 114.64, 110.87, 69.70, 57.68, 54.77, 52.97, 34.84, 33.79,27.97 ppm

PREPARATION 115

[S,[R*,S*(E)]]-N-(2-hydroxy-1-methyl-2-phenylethyl)-methyl-N-pentenamide (Formula NNN-3) See Chart NNN

A 250-mL, three-necked, round-bottomed flask with nitrogen inlet and addition funnel is charged with the compound of formula NNN-1 (6.6 g) (prepared from the treatment of commercially available trans-2-pentenoic acid with oxalyl chloride) and tetrahydrofuran (80 mL). The addition funnel is charged with a solution of (1R,2S)-ephedrine of formula NNN-2 (7.2 g) and triethylamine (6.0 mL) in tetrahydrofuran (15 mL), which is added dropwise to the reaction mixture. After stirring an additional hour, the reaction mixture is poured into 200 mL of ethyl acetate, washed with three 25-mL portions of water, and concentrated in vacuo to yield 13.5 g of an oil. Column chromatography on 100 g silica (elution with 10–100% ethyl acetate-hexane) yields 10.75 g of the title compound as a colorless oil.

Physical characteristics are as follows:

HRMS found: 248.1652.

PREPARATION 116

[1R-[1R*(R*)2S*]]-3-Amino-β-ethyl-N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl-benzenepropanamide (Formula NNN-4) See Chart NNN

A 50-mL, three-necked round-bottomed flask with a nitrogen inlet is charged with the title compound of Preparation 115 (0.247 g) and 5 mL of t-butyl methyl ether and cooled to 0° C. Propyl magnesium chloride (0.55 mL of 2.0M solution in ether) is added dropwise, and the reaction mixture is stirred for an additional 15 min. 3-[Bis(trimethylsilyl) amino]phenylmagnesium chloride (2.0 mL of 1.0M solution in tetrahydrofuran, 2.0 mmol) is added dropwise, and the resulting mixture is stirred for an additional 2 h at 0° C. and 1 h at room temperature. The reaction mixture is then

quenched with saturated aqueous ammonium chloride solution (pH adjusted to 8 with ammonium hydroxide) and partitioned between 100 mL of ethyl acetate and 5 mL of water. The organic layer is separated, washed with additional ammonium chloride solution and water, and concentrated in vacuo to give 0.72 g of a yellow oil. The crude oil is then dissolved in chloroform, and silica gel is added to the solution. The resulting mixture is stirred at room temperature for 1.5 h, then filtered through Celite, rinsing with methanol, and concentrated in vacuo to give 0.38 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 20–100% ethyl acetate-hexane) yields 0.174 g of the title compound as an oil.

Physical characteristics are as follows:

HRMS found: 340.2162.

PREPARATION 117

[1R-[1R*(R*)2S*]]-3-[bis(phenylmethyl)amino]-b-ethyl-N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methylbenzenepropanamide (Formula NNN-5) See Chart NNN

A 50-mL, three-necked, round-bottomed flask with a condenser fitted with a nitrogen inlet is charged with the title product of Preparation 116 (0.548 g) in 8 mL of acetonitrile. Sodium carbonate (0.375 g) and benzyl bromide (0.42 mL) are added, and the reaction mixture is heated to reflux for 4 h. The reaction mixture is then concentrated in vacuo and partitioned between 100 mL of ethyl acetate and 10 mL of water. The organic layer is separated, washed with another 10 mL of water, and concentrated in vacuo to give 1.0 g of a yellow oil. Column chromatography on 65 g of silica gel (elution with 20–100% ethyl acetate-hexane and 5% methanol-methylene chloride) yields 0.447 g of the title compound as a pale yellow oil.

Physical characteristics are as follows:

HRMS found: 520.3102.

PREPARATION 118

1-phenyl-6,6,6-trifluoro-3-hexanol (Formula PPP-2) Refer to Chart PPP

To a stirred solution of 4.0 g of ethyl 4,4,4-trifluorobutyrate of formula PPP-1 in 25 mL of tetrahydrofuran at −70° C. 24 mL of DiBAL-H (1M in toluene) is added dropwise and the solution stirred for 90 min. In a separate flask containing 680 mg of magnesium turnings and 5 mL of tetrahydrofuran is added 1-phenyl-2-bromoethane in 20 mL of tetrahydrofuran at a rate to maintain reflux. Heating of the mixture is continued for an additional 1 h, then cooled to room temperature and added via cannula to the DiBAL-H reaction above. The resulting white suspension is stirred 30 min at −70° C. and then allowed to warm to room temperature. The reaction is quenched with saturated aqueous ammonium chloride, diluted with 1N hydrochloric acid to dissolve the precipitated salts and extracted with ethyl acetate. The organic layers are combined, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product is flash chromatographed on silica gel eluting with 20% ethyl acetate in hexane to give 2.0 g of the title compound as a colorless oil.

Physical characteristics are as follows:

HRMS: 232.1088

IR (neat liquid): 3385, 2950, 1455, 1255, 1140, 700 cm^{-1}.

PREPARATION 119

1-phenyl-6,6,6-trifluoro-3-hexanone (Formula PPP-3) Refer to Chart PPP.

To a solution of 0.48 mL of oxalyl chloride in 10 mL of dichloromethane at −60° C. is added dropwise 0.81 mL of dimethylsulfoxide. The solution is stirred for 5 min then treated with 860 mg of 1-phenyl-6,6,6-trifluoro-3-hexanol of formula PPP-2 of Preparation 118 in 5 mL of dichloromethane and stirred for 15 min. Triethylamine (1.5 mL) is added, the mixture is allowed to warm to room temperature, diluted with water and the layers separated. The aqueous layer is extracted with dichloromethane, the organic layers combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting oil is flash chromatographed on silica gel to give 600 mg of the title compound as an oil.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$): δ7.2–7.3, 2.9, 2.7, 2.6, 2.4.

^{13}C NMR ($CDCl_3$): δ206, 140, 129, 128, 126, 125, 44, 35, 30, 28.

PREPARATION 120

5,6-dihydro-4-hydroxy-6-phenethyl-6-(3',3',3'-trifluoropropyl)-2H-pyran-2-one (Formula PPP-4) Refer to Chart PPP

A suspension of 350 mg of 50% sodium hydride in 10 mL of tetrahydrofuran at 0° C. is treated dropwise with 0.78 mL of methyl acetoacetate. After stirring 30 min, 4.5 mL of 1.6M n-butyllithium in hexane is added and stirring continued for 15 min. A solution of 840 mg of 1-phenyl-6,6,6-trifluoro-3-hexanone in 5 mL of tetrahydrofuran of formula PPP-3 of Preparation 119, is added, stirred at 0° C. for 15 min, then allowed to warm to room temperature and stirred for 1 h. The reaction mixture is quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layers are washed with water and brine, concentrated in vacuo, then dissolved in 20 mL of tetrahydrofuran. The solution is diluted with 60 mL of water and treated with 20 mL of 1N sodium hydroxide, stirred for 3 h at room temperature, concentrated in vacuo to remove the tetrahydrofuran, cooled to 5° C., and acidified with concentrated hydrochloric acid. The mixture is extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered and concentrated. The crude material is flash chromatographed on silica gel eluting with 30% ethyl acetate in hexane to give 870 mg of the title compound.

Physical characteristics are as follows:

ANAL: C, 61.14, H, 5.45.

PREPARATION 121

[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(3,3,3 -trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl] phenyl-carbamic acid, phenylmethylester (Formula QQQ-3 where R_1=t-Bu) Refer to Chart QQQ

The title compound of Preparation 120 (850 mg) in 25 mL of tetrahydrofuran at 0° C. is treated with 750 mg of aluminum trichloride, stirred 15 min, and then 700 mg of 3-benzyloxycarbonylaminobenzaldehyde is added. The mixture is allowed to stir at room temperature for 2 h then treated with 2 g of sodium carbonate monohydrate and 0.1 mL of water, stirred for 30 min, and filtered through celite washing the filter cake with tetrahydrofuran. The filtrate is concentrated in vacuo. The resulting material is dissolved in 25 mL of tetrahydrofuran and 285 mg of cuprous bromide-dimethylsulfide complex is added and the mixture stirred for 15 min before adding 11 mL of 1M t-butylmagnesium bromide in tetrahydrofuran dropwise over 15–20 min. The resulting brown mixture is stirred an additional 15 min then quenched at 0° C. with 50 mL of water. The layers are separated and the aqueous layer acidified with concentrated hydrochloric acid to dissolve inorganic salts and then extracted with ethyl acetate. The combined organic layers are washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Flash

chromatography on silica gel eluting with ethyl acetate in hexane gives 1.19 g of the title compound as a white to buff colored foam.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$): δ7.1–7.7, 6.7, 6.5, 4.4, 1.8–2.8, 1.16.

HRMS: 609.2711.

PREPARATION 122

Preparative resolution of [3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl-carbamic acid, phenylmethylester (Formula QQQ-3 where R_1=t-Bu) into 4 isomers, 3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(R or S)-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethyl-propyl]phenyl-carbamic acid, phenylmethylester (Formulas QQQ-4-7 where R_1 is t-Bu) Refer to Chart QQQ

The first phase of the resolution is accomplished with a 5.1×25 cm (R,R)Whelk-O 1 column eluted with 15% (V/V) isopropanol in hexane at 99 mL/min. ((R,R)Whelk-O 1 is a registered trademark of Regis Technologies, Inc., Morton Grove, Ill. 60053.) The peaks eluting at approximately 54 and 87 min are, respectively, pure Isomer 3 and Isomer 2 as judged from System A, below. The mixture of unresolved Isomer 1 and Isomer 4 eluted at approximately 64 minutes and is further treated as described below.

In the second phase of the resolution, the mixture from above that elutes near 64 minutes is injected onto a 2.1×25 cm Chiralcel OD column (Chiral Technologies, Inc.) and eluted with 35% isopropanol in hexane (V/V) at 8 mL/min. The peaks that elute near 8.7 and 23.9 minutes are, respectively, Isomer 1 and Isomer 4.

In both phase of the resolution of enantiomers, fractions are pooled after assay with System A and pools are concentrated to dryness on a rotary evaporator at 30 mm and a bath set at 50° maximum.

The four constituent enantiomers are (in order of elution from system A) designated (Peak #1), (Peak #2), (Peak #3) and (Peak #4). System A consists of a 0.46×25 cm Chiralcel OD-H column eluted at 1.0 mL/min with 20% isopropanol in hexane (V/V). (Chiralcel OD-H is a registered trademark of Chiral Technologies, Inc., Exton Pa. 19341.)

PREPARATION 123

3(R or S)-[1-(3-aminophenyl)-2,2-dimethylpropyl]-4-hydroxy-5,6-dihydro-6-(R or S)-phenethyl-6-(3,3,3-trifluoropropyl)-2H-pyran-2-one (Formula QQQ-8, R_1=t-Bu) Refer to Chart QQQ

A solution of 210 mg of the compound identified as peak 1 from Preparation 122 in 10 mL of methanol is treated with 400 mg of ammonium formate and 40 mg of 10% palladium on charcoal, stirred 2 h, filtered through celite washing the filter cake with methanol. The filtrate is diluted with ethyl acetate and washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 160 mg of the title compound as a white foam.

Physical characteristics are as follows:

^{1}H NMR (CD_3OD): δ6.9–7.3, 6.6, 4.1, 2.6–2.7, 1.9–2.4, 1.0.

TLC (silica gel GF): R_f=0.24 (40% ethyl acetate in hexane).

EXAMPLE 266

5-cyano-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide (Formula QQQ-13, R_1 is t-Bu [R_2 is [5-cyano-2-pyridinyl]) Refer to Chart QQQ

A solution of the title product of Preparation 123 (50 mg), pyridine (30 mL), and 5-cyano-pyridine-2-sulfonyl chloride (30 mg) in dichloromethane at 0° C. is stirred for 2 h. The crude reaction mixture is chromatographed on silica gel to give the title compound as a white amorphous solid.

Physical characteristics are as follows:

FAB HRMS: 642.2267.

EXAMPLE 267

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(R or S)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula QQQ-13, R_1 is t-Bu, [R_2 is 1-methyl-4-imidazolyl]) Refer to Chart QQQ

Following the procedure described in EXAMPLE 266 and substituting 5-cyano-2-pyridine sulfonyl chloride with 1-methylimidazole-4-sulfonyl chloride the title compound is prepared.

Physical characteristics are as follows:

HRMS: 619.2298

EXAMPLE 268

5-amino-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide (Formula QQQ-13, R_1=t-Bu, [R_2 is 5-amino-2-pyridinyl]) Refer to Chart QQQ

A solution of the title product of Preparation 123 (50 mg), pyridine (30 μL), and 5-nitro-pyridine-2-sulfonyl chloride (30 mg) in dichloromethane at 0° C. is stirred for 2 h. The crude reaction mixture is chromatographed on silica gel to give the sulfonamide as a white amorphous solid. The white solid is dissolved in 4 mL of methanol and treated with 25 mg of ammonium formate and 5 mg of 10% palladium on carbon, stirred for 1 h at room temperature, diluted with water and extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give the title compound as an off-white amorphous solid.

Physical characteristics are as follows:

FAB HRMS: 632.2393.

PREPARATION 124

3(R or S)-[1-(3-aminophenyl)-2,2-dimethyl-propyl]-4-hydroxy-5,6-dihydro-6(S or R)-phenethyl-6-(3',3',3'-trifluoropropyl)-2H-pyran-2-one (Formula QQQ-9, [R_1 is t-Bu]) Refer to Chart QQQ

Following the procedure described in Preparation 123 beginning with the compound isolated from peak 2 from Preparation 122 and using starting materials and reagents known and available to one of ordinary skill in organic synthesis the title compound is prepared.

Physical characteristics are as follows: 1H NMR (CD_3OD): δ6.9–7.3, 6.6, 4.1, 2.6–2.7, 1.9—2.4, 1.0.

TLC (silica gel GF): R_f=0.24 (40% ethyl acetate in hexane).

EXAMPLE 269

5-cyano-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide (Formula QQQ-14, R_1 is t-Bu [R_2 is 5-cyano-2-pyridinyl]) Refer to Chart QQQ

A solution of the title product of Preparation 124 (50 mg), pyridine (30 μL), and 5-cyanopyridine-2-sulfonyl chloride (30 mg) in dichloromethane at 0° C. is stirred for 2 h. The crude reaction mixture is chromatographed on silica gel to give the title compound as a white amorphous solid.

Physical characteristics are as follows:
FAB HRMS: 642.2260.

EXAMPLE 270

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(R or S)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula QQQ-14, R_1 is t-Bu [R_2 is 1-methyl-4-imidazolyl]) Refer to Chart QQQ

Following the procedure described in Example 266 substituting 5-cyano-2-pyridine sulfonyl chloride with 1-methylimidazole-4-sulfonyl chloride the title compound is prepared.

Physical characteristics are as follows:
HRMS: 619.2362

EXAMPLE 271

5-amino-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide (Formula QQQ-14, R_1 is t-Bu [R_2 is 5-amino-2-pyridinyl]) Refer to Chart QQQ

Following the procedure described in Example 268 the title compound is prepared.

Physical characteristics are as follows:
FAB HRMS: 632.2387

PREPARATION 125

3-(S or R)-[1-(3-aminophenyl)-2,2-dimethyl-propyl]-4-hydroxy-5,6-dihydro-6-(R or S)-phenethyl-6-(R or S)-(3',3',3'-trifluoropropyl)-2H-pyran-2-one (Formula QQQ-10 [R_1 is t-Bu]) Refer to Chart QQQ

Following the procedure described in Preparation 123 beginning with the compound isolated from peak 3 from Preparation 122 and using starting materials and reagents known and available to one of ordinary skill in organic synthesis the title compound is prepared.

Physical characteristics are as follows:
^{1}H NMR (CD_3OD): δ6.9–7.3, 6.6, 4.1, 2.6–2.7, 1.9–2.4, 1.0.

TLC (silica gel GF): R_f=0.24 (40% ethyl acetate in hexane).

EXAMPLE 272

5-cyano-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide (Formula QQQ-15, R_1 is t-Bu, [R_2 is 5-cyano-2-pyridinyl]) Refer to Chart QQQ

A solution of the title product of Preparation 125 (50 mg), pyridine (30 mL), and 5-cyanopyridine-2-sulfonyl chloride (30 mg) in dichloromethane at 0° C. is stirred for 2 h. The crude reaction mixture is chromatographed on silica gel to give the title compound as a white amorphous solid.

Physical characteristics are as follows:
FAB HRMS: 642.2254

EXAMPLE 273

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(R or S)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula QQQ-15, R_1 is t-Bu, [R_2 is 1-methyl-4-imidazolyl]) Refer to Chart QQQ

Following the procedure described in Example 266 substituting 5-cyano-2-pyridine sulfonyl chloride with 1-methylimidazole-4-sulfonyl chloride the title compound is prepared.

Physical characteristics are as follows:
FAB HRMS: 642.2397

EXAMPLE 274

5-amino-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide (Formula QQQ-15, R_1 is t-Bu [R_2 is 5-amino-2-pyridinyl]) Refer to Chart QQQ

Following the procedure described in Example 268 the title compound is prepared.

Physical characteristics are as follows:
FAB HRMS: 632.2393

PREPARATION 126

3-(S or R)-[1-(3-aminophenyl)-2,2-dimethyl-propyl]-4-hydroxy-5,6-dihydro-6 (S or R)-phenethyl-6-(3',3',3'-trifluoropropyl)-2H-pyran-2-one (Formula QQQ-11 [R_1 is t-Bu]) Refer to Chart QQQ

Following the procedure described in Preparation 123 beginning with the compound isolated from peak 4 from Preparation 122 and using starting materials and reagents known and available to one of ordinary skill in organic synthesis the title compound is prepared.

Physical characteristics are as follows:
^{1}H NMR (CD_3OD): δ6.9–7.3, 6.6, 4.1, 2.6–2.7, 1.9–2.4, 1.0.

TLC (silica gel GF): R_f=0.24 (40% ethyl acetate in hexane)

EXAMPLE 275

5-cyano-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide (Formula QQQ-16, R_1 is t-Bu, [R_2 is 5-cyano-2-pyridinyl]) Refer to Chart QQQ

A solution of the title product of Preparation 126 (50 mg), pyridine (30 mL), and 5-cyanopyridine-2-sulfonyl chloride (30 mg) in dichloromethane at 0° C. is stirred for 2 h. The crude reaction mixture is chromatographed on silica gel to give the title compound as a white amorphous solid.

Physical characteristics are as follows:
FAB HRMS: 642.2248.

EXAMPLE 276

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(R or S)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula QQQ-16, R_1 is t-Bu, [R_2 is 1-methyl-4-imidazolyl]) Refer to Chart QQQ

Following the procedure described in Example 266 substituting 5-cyano-2-pyridine sulfonyl chloride with 1-methylimidazole-4-sulfonyl chloride the title compound is prepared.

Physical characteristics are as follows:
FAB HRMS: 620.2403

EXAMPLE 277

5-amino-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide (Formula QQQ-16, R_1 is t-Bu, [R_2 is 5-amino-2-pyridinyl]) Refer to Chart QQQ

Following the procedure described in Example 268 the title compound is prepared.

Physical characteristics are as follows:
FAB HRMS: 632.2406

EXAMPLE 278

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-[6-(R or S)-propyl]-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide

Following procedures analogous to those described above and using Isomer 2 of Preparation 143 the title compound is prepared.

Physical characteristics are as follows:

FAB HRMS: 562.2527.

EXAMPLE 279

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide

Following procedures analogous to those described above and using Isomer 1 of Preparation 143 the title compound is prepared.

Physical characteristics are as follows:

FAB HRMS: 562.2528.

PREPARATION 127

2-Mercapto-4-trifluoromethylpyridine

To 1.0 g of 2-chloro-4-trifluoromethylpyridine (Lancaster Chemical Co) is added 10 ml of absolute ethanol and 417 mg of thiourea. The reaction mixture is heated at reflux for 4 hours and 1.25 ml of a solution of 7.44 g KOH in 20 ml of water is added. The solution is heated at reflux for an additional 1 hour. The reaction solution is cooled and poured into 100 ml of a 0.1N NaOH solution. The resulting solution is extracted three times with 100 ml of methylene chloride and the resulting aqueous solution is acidified to pH 4 by addition of glacial acetic acid. The aqueous solution is extracted three times with 100 ml of methylene chloride and the organic solution is dried over anhydrous sodium sulfate. Filtration followed by evaporation to dryness gives 501 mg of a yellow crystalline solid.

Physical characteristics are as follows:

Found C:40.22; H:2.33; N:8.07; S:17.59

HRMS: 179.0019

PREPARATION 128

2-Chlorosulfonyl-4-trifluoromethylpyridine

To 425 mg of 2-mercapto-4-trifluoromethylpyridine of Preparation 127 is added 10 ml of 1N aqueous HCl. The reaction mixture is cooled to 0° C. and Cl_2 gas is bubbled into the cold reaction mixture for 15 minutes. The reaction mixture is filtered and the resulting solid is washed well with water. The white solid is dissolved in methylene chloride and is washed twice with saturated aqueous $NaHCO_3$ followed by one wash with water. After drying the organic solution over sodium sulfate (anhydrous), the solution is filtered and evaporated to dryness to give 300 mg of 2-chlorosulfonyl-4-trifluoromethylpyridine which is used directly without further purification, and stored at −78° C. until ready for use.

PREPARATION 129

2-Chlorosulfonyl-5-trifluoromethylpyridine

Substituting 2-mercapto-5-trifluoromethylpyridine for 2-mercapto-4-trifluoromethylpyridine in the reaction above in Preparation 128 gives 2-chlorosulfonyl-5-trifluoromethylpyridine as a colorless oil which slowly crystallizes. This material is used without further purification and stored at −78° C. until ready for use.

PREPARATION 130

3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6,6-di-n-propyl-2H-pyran-3-yl]-propyl]phenyl-carbamic acid, (Formula SSS-1; R_1 is ethyl; Refer to Chart SSS)

To 7.2 g of $AlCl_3$ at −70° C., under N_2, is added 180 ml of THF. The mixture is allowed to stir at 0° C. for 15 minutes and 5.38 g of Formula SSS-A; Refer to Chart SSS, prepared by procedures analogous to those described in Preparation 17, is added. The reaction mixture is stirred for 15 minutes and 6.88 g of 3-aminoCbZ-benzaldehyde (Formula SSS-B; Refer to Chart SSS) is added. The reaction mixture is stirred for 15 minutes at 0° C. followed by 3 hours at room temperature. The reaction is cooled to 0° C. and 35 g of sodium carbonate monohydrate is added, with vigorous stirring, followed by 1.6 ml of water. After stirring at 0° C. for an additional 15 minutes, 120 ml of THF is added and the mixture filtered through celite. The celite is washed well with THF and the THF solution is evaporated to dryness under vacuum to an amber foam. The residue is dissolved in 180 ml of THF, the solution is cooled to −5° C. and 3.2 g of $CuBr.Me_2S$ added. The mixture is stirred for 15 minutes and 65 ml of a 2M ethylmagnesium chloride in THF solution is added, dropwise, with temperatures not rising above 0° C. The reaction is allowed to stir for an additional 15 minutes and 9 ml of water is slowly added followed by 45 ml of 1N HCl. These additions are done at 0° C. The reaction mixture is poured into 2 L of ethyl ether and 200 ml of water is added. The aqueous layer is separated and the organic layer is extracted three times with 10% aqueous ammonium carbonate followed by once with water. The organic solution is dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give 10.2 g of a crude amorphous foam. This crude material is chromatographed over silica gel using 2% ethyl acetate in methelene chloride as eluent to give 4.74 g of 3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6,6-di-n-propyl-2H-pyran-3-yl]-propyl]phenyl-carbamic acid.

PREPARATION 130A

3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl)-2H-pyran-3-yl]-propyl]-phenyl-carbamic acid (Formula RRR-1; R_1 is ethyl; Refer to Chart RRR)

Following the procedure of Preparation 130 beginning with the compound from Preparation 17 the title compound is prepared.

Physical characteristics are as follows:

^1H NMR (CD_3OD): δ6.9–7.5, 5.1, 4.0, 1.4–2.7, 0.9.

TLC (silica gel GF): Rf=0.28, 30% ethyl acetate in hexane.

PREPARATION 131

Preparative chiral resolution of 3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6,6-di-n-propyl-2H-pyran-3-yl]-propyl] phenyl-carbamic acid (Formula SSS-1; R_1 is ethyl; Refer to Chart SSS) to give two isomers of 3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6,6-di-n-propyl-2H-pyran-3-yl]-propyl]phenyl-carbamic acid (Formulas SSS-3 and SSS-4; R_1 is ethyl; Refer to Chart SSS).

Samples of the title compound of Preparation 130 are injected onto a 2.1×25 cm Chiralcel OD column and eluted with 20% isopropanol (V/V) in hexane at 10 mL/min. The material eluting near 19.1 minutes is 3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6,6-di-n-propyl-2H-pyran-3-yl]-propyl]phenyl-carbamic acid, (α)25D +26° (methanol), (Formula SSS-3; Refer to Chart SSS) (peak 1) and that eluting near 37.7 minutes is 3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6,6-di-n-propyl-2H-pyran-3-yl]-propyl] phenyl-carbamic acid ($(\alpha)^{25}_D$ −27° (methanol), (Formula SSS-4; Refer to Chart SSS) (peak 2). The pools are concentrated separately on a rotary evaporator (ca. 30 mm, bath at 50° maximum) to give white amorphous solids.

PREPARATION 132

3(R or S)-[1-(3-aminophenyl)-propyl]-4-hydroxy-5,6-dihydro-6,6-dipropyl-2H-pyran-2-one (Formula SSS-5; R_1 is ethyl; Refer to Chart SSS)

To 1.04 g of 3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6,6-di-n-propyl-2H-pyran-3-yl]-propyl]phenyl-carbamic acid (Formula SSS-3; Refer to Chart SSS) of Preparation 131, the compound identified as peak 1 from the chiral resolution of the product of Preparation 131, is added 20 ml of methanol and 1.29 g of ammonium formate. When dissolution is complete, 275 mg of 10% Pd/C is added and the reaction mixture is stirred at room temperature for 60 minutes. The reaction mixture is filtered (celite) and the methanolic solution is evaporated to dryness to give a crude solid. The crude solid is partitioned between methylene chloride and water. The organic layer is washed twice with water and dried over anhydrous sodium sulfate. The methylene chloride solution is filtered and evaporated to dryness to give 625 mg of 3(R or S)-[1-(3-aminophenyl)-propyl]-4-hydroxy-5,6-dihydro-6,6-dipropyl-2H-pyran-2-one as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 331

$(\alpha)^{25}_{D}$ +38° (c=0.3715, methanol).

PREPARATION 133

3(R or S)-[1-(3-aminophenyl)-propyl]-4-hydroxy-5,6-dihydro-6,6-di-n-propyl-2H-pyran-2-one (Formula SSS-6; R_1 is ethyl; Refer to Chart SSS)

To 825 mg of 3(R or S)-[1-(3-aminophenyl)-propyl]-4-hydroxy-5,6-dihydro-6,6-dipropyl-2H-pyran-2-one (Formula SSS-4; Refer to Chart SSS), of Preparation 131, the compound identified as peak 2 from the chiral resolution of the product of Preparation 131, is added 20 ml of methanol and 1.02 g of ammonium formate. When dissolution is complete, 210 mg of 10% Pd/C is added and the reaction mixture is stirred at room temperature for 60 minutes. The reaction mixture is filtered (celite) and the methanolic solution is evaporated to dryness. The crude solid is partitioned between methylene chloride and water. The organic layer is washed twice with water and dried over anhydrous sodium sulfate. The methylene chloride solution is filtered and evaporated to dryness to give 483 mg of title compound as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 331

$(\alpha)^{25}_{D}$ −39° (c=0.2680, methanol).

EXAMPLE 280

5-Trifluoromethyl-N-[3-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula SSS-9; R_1 is ethyl; R_2 is 5-trifluoromethylpyridine; Refer to Chart SSS)

The title compound of Preparation 130 is deprotected as in Preparation 132 to give the compound of formula SSS-2. To 132 mg of formula SSS-2 is added 15 ml of methylene chloride and 66 microliters of pyridine. The reaction solution is cooled to −5° C. and 98 mg of 2-chlorosulfonyl-5-trifluoromethylpyridine (product of Preparation 129) is added. After stirring at 0° C. for 60 minutes the solution is placed on a silica gel column and eluted with 10% ethyl acetate in methylene chloride until the 5-trifluoromethyl-N-[3-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide is collected. Rf=0.6 in 10% ethyl acetate in methylene chloride. Evaporation of the organic solution to dryness gives 177 mg of 5-trifluoromethyl-N-[3-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide

Physical characteristics are as follows:

MS(EI): 540, 497, 411, 401, 383, 342, 331, 197, 174, 146, 133.

HRMS: 540.1938

Rf=0.6 in 10% ethyl acetate in methylene chloride.

^{1}H NMR(MeOD): δ8.91, 8.21–8.19, 7.12, 6.98–6.96, 6.86–6.83, 3.85–3.79, 2.46, 2.10–1.98, 1.84–1.75, 1.58–1.47, 1.27–1.15, 0.82–0.72 ppm

EXAMPLE 281

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula SSS-7; R_1 is ethyl; R_2 is 5-trifluoromethylpyridine; Refer to Chart SSS)

To 66 mg of the title product from Preparation 132 (Formula SSS-5; Chart SSS) is added 8 ml of methylene chloride and 33 microliters of pyridine. The reaction solution is cooled to −5° C. and 49 mg of 2-chlorosulfonyl-5-trifluoromethylpyridine (product of Preparation 129) is added. After stirring at 0° C. for 60 minutes the solution is placed on a silica gel column and eluted with 10% ethyl acetate in methylene chloride until the 5-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide is collected. Rf=0.6 in 10% ethyl acetate in methylene chloride. Evaporation of the organic solution to dryness gives 69 mg of the title compound.

Physical characteristics are as follows:

MS(EI): 540, 497, 411, 401, 383, 342, 331, 197, 174, 146, 133.

Rf=0.6 in 10% ethyl acetate in methylene chloride

^{1}H NMR(MeOD): δ8.91, 8.21–8.19, 7.12, 6.98–6.96, 6.86–6.83, 3.85–3.79, 2.46, 2.10–1.98, 1.84–1.75, 1.58–1.47, 1.27–1.15, 0.82–0.72 ppm

EXAMPLE 282

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula SSS-8; R_1 is ethyl; R_2 is 5-trifluoromethylpyridine; Refer to Chart SSS)

Following the procedure of Example 281 but substituting the product of Preparation 133 (formula SSS-6) gives 5-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 540, 497, 411, 401, 383, 342, 331, 197, 174, 146, 133.

Rf=0.6 in 10% ethyl acetate in methylene chloride

^{1}H NMR(MeOD): δ8.91, 8.21–8.19, 7.12, 6.98–6.96, 6.86–6.83, 3.85–3.79, 2.46, 2.10–1.98, 1.84–1.75, 1.58–1.47, 1.27–1.15, 0.82–0.72 ppm

EXAMPLE 283

4-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula SSS-7; R_1 is ethyl; R_2 is 4-trifluoromethylpyridine; Refer to Chart SSS)

Following the procedure of Example 281 but substituting the product of Preparation 128 for the pyridylsulfonylchloride gives 4-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl-propyl]-phenyl]-2-pyridinesulfonamide as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 146, 145, 139, 133, 71, 57, 55, 43, 41

HRMS: 540.1902

EXAMPLE 284

4-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula SSS-8; R_1 is ethyl; R_2 is 4-trifluoromethylpyridine; Refer to Chart SSS)

Following the procedure of Example 282 but substituting the product of Preparation 128 for the pyridylsulfonylchloride gives 4-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 146, 145, 139, 133, 71, 57, 55, 43, 41

HRMS: 540.1896

EXAMPLE 285

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide (Formula TTT-6; R_1 is t-butyl; R_2 is n-propyl; R_3 is 5-trifluoromethyl-2-pyridinyl; Refer to Chart TTT)

Following the procedure of Example 281 but using Isomer 1 of Preparation 144 (Formula TTT-4; Chart TTT; R_1 is t-butyl, R_2 is n-propyl) gives 5-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide as an amorphous solid.

Physical characteristics are as follows:

MS(EI): 163, 162, 147, 146, 69, 57, 56, 43, 41

HRMS: 568.2213

EXAMPLE 286

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]1-2-pyridinesulfonamide (Formula TTT-7; R_1 is t-butyl; R_2 is n-propyl; R_3 is 5-trifluoromethylpyridine; Refer to Chart TTT)

Following the procedure of Example 281 but substituting Isomer 2 of Preparation 144 (Formula TTT-5; Chart TTT; R_1 is t-butyl; R_2 is n-propyl) gives 5-trifluoromethyl-N-[3-[1(R or S)-4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide as an amorphous solid.

Physical characteristics are as follows:

HRMS: 568.2237

EXAMPLE 287

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula TTT-6; R_1 is ethyl; R_2 is phenyl; R_3 is 5-trifluoromethylpyridine; Refer to Chart TTT)

Following the procedure of Example 281 but using Isomer 1 of Preparation 145 (Formula TTT-4; Chart TTT; R_1 is ethyl; R_2 is phenyl) gives 5-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide as an amorphous solid.

Physical characteristics are as follows:

MS(EI): 665, 647, 456, 455, 333, 134, 133, 117, 105, 91

EXAMPLE 288

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula TTT-7; R_1 is ethyl; R_2 is phenyl; R_3 is 5-trifluoromethylpyridine; Refer to Chart TTT)

Following the procedure of Example 281 but substituting Isomer 2 of Preparation 145 (Formula TTT-5; Chart TTT; R_1 is ethyl; R_2 is phenyl) gives 5-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide as an amorphous solid.

Physical characteristics are as follows:

HRMS: 665.2300

MS(EI): 665, 647, 456, 455, 333, 134, 133, 117, 105, 91

EXAMPLE 289

4-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula TTT-6; R_1 is ethyl; R_2 is phenyl; R_3 is 4-trifluoromethylpyridine; Refer to Chart TTT)

Following the procedure of Example 281 but substituting Isomer 1 of Preparation 145 (Formula TTT-4; Chart TTT; R_1 is ethyl; R_2 is phenyl) gives 5-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide as an amorphous solid.

Physical characteristics are as follows:

MS(EI): 666, 665, 647, 134, 133, 117, 105, 91

HRMS: 665.2306

EXAMPLE 290

4-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula TTT-7; R_1 is ethyl; R_2 is phenyl; R_3 is 4-trifluoromethylpyridine; Refer to Chart TTT)

Following the procedure of Example 281 but substituting Isomer 2 of Preparation 145 (Formula TTT-5; Chart TTT; R_1 is ethyl; R_2 is phenyl) gives 4-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide as an amorphous solid.

Physical characteristics are as follows:

HRMS: 665.2306

MS(EI): 666, 665, 647, 134, 133, 117, 105, 91

EXAMPLE 291

4-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide (Formula TTT-6; R_1 is t-butyl; R_2 is methyl; R_3 is 4-trifluoromethylpyridine; Refer to Chart TTT)

Following the procedure of Example 283 but substituting Isomer 1 of Preparation 144 (Formula TTT-4; Chart TTT; R_1 is t-butyl; R_2 is methyl) gives 4-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide as an amorphous solid.

Physical characteristics are as follows:

MS(EI): 525, 512, 428, 411, 302, 284, 258, 146, 57

HRMS: 568.2209

EXAMPLE 292

4-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide (Formula TTT-7; R_1 is t-butyl; R_2 is methyl; R_3 is 4-trifluoromethylpyridine; Refer to Chart TTT)

Following the procedure of Example 283 but substituting Isomer 2 of Preparation 144 (Formula TTT-5; Chart TTT; R_1 is t-butyl; R_2 is methyl) gives 4-trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide as an amorphous solid.

Physical characteristics are as follows:

MS(EI): 569, 551, 511, 493, 439, 371, 360, 303, 284, 161, 139

HRMS (MI+H$^+$): 569.2297

PREPARATION 134

N-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl] phenylcarbamic acid, phenylmethyl ester (Formula RRR-1; R_1 is t-butyl; Refer to Chart RRR)

To 4.8 g of $AlCl_3$ at −70° C., under N_2, is added 120 ml of THF. The mixture is allowed to stir at 0° C. for 15 minutes and 4.68 g of (formula RRR-A) of Preparation 17 is added. The reaction mixture is stirred for 15 minutes and 4.59 g of 3-aminoCbZ-benzaldehyde (formula RRR-B) is added. The reaction mixture is stirred for 15 minutes at 0° C. followed by 3 hours at room temperature. The reaction is cooled to 0° C. and 26 g of sodium carbonate monohydrate (0.21M) is added, with vigorous stirring, followed by 1.08 ml of water. After stirring at 0° C. for an additional 15 minutes, the mixture is treated with 120 ml of THF and filtered through celite. The celite is washed well with THF and the THF solution is evaporated to dryness under vacuum to an amber foam. The residue is dissolved in 120 ml of THF, the solution is cooled to −5° C. and 2.1 g of $CuBr.Me_2S$ added. The mixture is stirred for 15 minutes and 65 mL of a 1M t-butylmagnesium chloride in THF solution is added, dropwise, with temperatures not rising above 0° C. The reaction is allowed to stir for an additional 15 minutes at 0° C. and 6 ml of water is slowly added followed by 30 ml of 1N HCl. The reaction mixture is poured into 1.3 L of ethyl ether. The aqueous layer is separated and the organic layer is extracted three times with 10% aqueous ammonium carbonate followed by once with water. The organic solution is dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give an amorphous foam. This crude material is chromatographed over silica gel using 30% ethyl acetate in hexane as eluent to give 6.15 g the title product.

PREPARATION 135

Preparative resolution of N-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl-carbamic acid, phenylmethyl ester (Formula RRR-1; R_1 is t-butyl) into four isomers, 3-(R or S)-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(R or S)-(2-phenethyl)-6-(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethyl-propyl]phenyl-carbamic acid, phenylmethyl ester (Formulas RRR-3 to 6; R_1 is t-butyl; Refer to Chart RRR)

The four constituent enantiomers are (in order of elution from system A) Isosmer 1 (Formula RRR-4; refer to Chart RRR), Isomer 2 (Formula RRR-3; refer to Chart RRR), Isomer 3 (Formula RRR-5; refer to Chart RRR), and Isomer 4 (Formula RRR-6; refer to Chart RRR). System A consists of a 0.46×25 cm Chiralcel OD-H column eluted at 0.5 mL/min with 20% isopropanol and 0.1% trifluoracetic acid in hexane (V/V). (Chiralcel OD-H is a registered trademark of Chiral Technologies, Inc., Exton Pa. 19341.)

The first phase of the resolution is accomplished with a 2.1×25 cm (R,R)Whelk-O 1 column eluted with 20% (V/V) isopropanol in hexane at 12 mL/min. ((R,R)Whelk-O 1 is a registered trademark of Regis Technologies, Inc., Morton Grove, Ill. 60053.) The peaks eluting at approximately 35 and 41 min are, respectively, a mixture of Isomer 3 and Isomer 4 and a mixture of Isomers 1 and 2 and as judged from System A, above. The two mixtures are further treated as below.

In the second phase of the resolution, the mixture from above that elutes near 41 minutes is injected onto a 2.1×25 cm Chiralcel OD column (Chiral Technologies, Inc.) and elutes with 15% isopropanol and 0.05% trifluoracetic acid in hexane (V/V) at 9.0 mL/min. The peaks that elute near 11.0 and 22.0 minutes are designated respectively, peaks 1 and 2 and as judged from System A.

In the final phase of the resolution, the mixture that elutes from the Whelk-O column near 35 minutes is injected onto a 2.2×25 cm Chiralcel OD column and elutes with 35% isopropanol and 0.1% trifluoroacetic acid (V/V) in hexane at 9.0 mL/min. The isomer that elutes near 9.7 minutes is designated peak 3 and the one that elutes near 16.6 minutes is designated peak 4.

PREPARATION 136

3-[1-(3-Aminophenyl)-2,2-dimethyl-propyl]-5,6-dihydro-4-hydroxy-6-phenethyl-6-n-propyl-pyran-2-one (Formula RRR-2, Refer to Chart RRR)

To 590 mg of 3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl] phenyl-carbamic acid of Preparation 134, is added 10 ml of methanol and 660 mg of ammonium formate. When all the reactants are dissolved, 140 mg of 10% Pd/C is added and the reaction is allowed to stir at room temperature for 60 minutes. The reaction is filtered (celite) and the filter pad is washed well with methanol and the methanol solution is evaporated under vacuum to a crude solid. The solid is partitioned between water and methylene chloride, and the methylene chloride layer is washed twice with water, dried over anhydrous sodium sulfate and evaporated to dryness to give 372 mg of 3-[1-(3-amino-pheny)-2,2-dimethyl-propyl] -5,6-dihydro-4-hydroxy-6-phenethyl-6-n-propyl-pyran-2-one. This material is identical to material described earlier (Formula T-4; refer to Chart T).

PREPARATION 137

3(R or S)-[1-(3-amino-phenyl)-2,2-dimethyl-propyl]-5,6-dihydro-4-hydroxy-6(R or S)-phenethyl-6(R or S)-propyl-pyran-2-one (Formula RRR-7; R_1 is t-butyl; Refer to Chart RRR)

Following the procedure of Preparation 136 but substituting the compound in Preparation 135 designated peak 2 for the compound of Preparation 134 gives 3(R or S)-[1-(3-amino-pheny)-2,2-dimethyl-propyl]-5,6-dihydro-4-hydroxy-6(R or S)-phenethyl-6(R or S)-propyl-pyran-2-one as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 421, 365, 164, 163, 147, 146, 118, 107, 91, 57.

HRMS: 421.2617

PREPARATION 138

3(R or S)-[1-(3-Amino-pheny)-2,2-dimethyl-propyl]-5,6-dihydro-4-hydroxy-6(R or S)-phenethyl-6(R or S)-propyl-pyran-2-one (Formula RRR-8; R_1 is t-butyl; Refer to Chart RRR)

Following the procedure of Preparation 136 but substituting the compound of Preparation 135 designated peak 1 for the compound of Preparation 134 gives 3(R or S)-[1-(3-amino-pheny)-2,2-dimethyl-propyl]-5,6-dihydro-4-hydroxy-6(R or S)-phenethyl-6(R or S)-propyl-pyran-2-one as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 421, 365, 164, 163, 147, 146, 118, 107, 91, 57.

EXAMPLE 293

5-Trifluoromethyl-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide (Formula RRR-15; R_1 is t-butyl; R_2 is 5-trifluoromethyl; Refer to Chart RRR).

Following the procedure of Example 281 but substituting the product of Preparation 136 for the product of Preparation 132 gives 5-trifluoromethyl-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 497, 411, 401, 383, 343, 331, 197, 174, 146, 133

HRMS: 540.1938

EXAMPLE 294

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide (Formula RRR-11; R_1 is t-butyl; R_2 is 5-trifluoromethyl; Refer to Chart RRR)

Following the procedure of Example 281 but substituting the product of Preparation 137 for the product of Preparation 132 gives 5-trifluoromethyl-N-[3 (R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 373, 355, 201, 146, 145, 118, 117, 91, 57.

HRMS:630.2394

EXAMPLE 295

5-Trifluoromethyl-N-[3 (R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide (Formula RRR-12; R_1 is t-butyl; R_2 is 5-trifluoromethyl; Refer to Chart RRR)

Following the procedure of Preparation 281 but substituting the product of Preparation 138 for the product of Preparation 132 gives 5-trifluoromethyl-N-[3(R or S)-(-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 373, 355, 201, 146, 145, 118, 117, 91, 57.

HRMS:630.2379

EXAMPLE 296

4-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide (Formula RRR-11, R_1 is t-butyl; R_2 is 4-trifluoromethyl; Refer to Chart RRR)

Following the procedure of Example 294 but substituting the product of Preparation 128 for the product of Preparation 129 gives 4-trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 633, 632, 631, 614, 613, 346, 201, 146, 91, 57

HRMS: 631.2444

EXAMPLE 297

4-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide (Formula RRR-12; R_1 is t-butyl; R_2 is 4-trifluoromethyl; Refer to Chart RRR)

Following the procedure of Example 295 but substituting the product of Preparation 128 for the product of Preparation 129 gives 4-trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 633, 632, 631, 614, 613, 346, 201, 146, 91, 57.

HRMS: 631.2450

EXAMPLE 298

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula RRR-11; R_1 is ethyl; R_2 is 5-trifluoromethyl; Refer to Chart RRR)

Following the procedure of Example 294 but substituting the product of Preparation 147A gives 5-trifluoromethyl-N-[3(R or S)-(-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl) phenyl]-2-pyridinesulfonamide as an amorphous foam.

Physical characteristics are as follows:

MS(EI): 605, 604, 603, 602, 586, 585, 393, 201, 133, 91

HRMS: 603.2153

EXAMPLE 298A

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide (Formula RRR-12; R_1 is ethyl; R_2 is 5-trifluoromethyl; Refer to Chart RRR)

Following the procedure of Example 294 but substituting the amine derived from Isomer 1 of Preparation 147 (derived following the procedure of Preparation 147A) gives the title compound as an amorphous foam.

Physical characteristics are as follows:

^{1}H NMR (CD_3OD): δ8.9, 8.2, 8.0, 7.0–7.3, 3.9, 2.4–2.7, 1.2–2.2, 0.8–1.0.

TLC (silica gel GF): Rf=0.19, 40% ethyl acetate in hexane.

PREPARATION 139

(5-Nitro-pyridin-2-yl)-isothiourea hydrochloride (Formula UUU-2) Refer to Chart UUU

A solution of 3.81 g of thiourea in 75 mL of hot absolute ethanol is treated with 7.61 g of 2-chloro-5-nitropyridine (Formula UUU-1) and is heated at reflux for 6 hours. The mixture is then cooled to 0° C. and the precipitated solid is collected. The solid is washed sequentially with cold absolute ethanol and chloroform. The solid is dried in vacuo to afford 6.91 g of the title product as a light brown solid.

Physical characteristics are as follows:

MP 175° C. (dec.)

^{1}H NMR (CD_3OD) δ7.9, 8.6, 9.4 ppm

PREPARATION 140

5-Nitro-2-thiopyridine (Formula UUU-3) Refer to Chart UUU

A solution of 1.65 g of sodium carbonate in 50 mL of water is treated with 2.35 g of the title compound of Preparation 139. The mixture is charged with a solution of 2.75 g of sodium hydroxide in 50 mL of water and the resulting mixture is warmed to room temperature. After stirring for 1 hour, the mixture is heated to 95° C. for 1 hour and finally cooled to room temperature. The aqueous mixture is extracted with two portions of diethyl ether and then carefully acidified with 6N aqueous hydrochloric acid. The orange precipitated solid is collected and washed sequentially with cold dilute aqueous hydrochloric acid and water. The solid is dried in vacuo to afford 1.27 g of the title product as an orange solid.

Physical characteristics are as follows:

MP 167°–170° C.

^{1}H NMR ($CDCl_3$—CD_3OD) δ7.4, 7.9, 8.5 ppm

PREPARATION 141

5-Nitro-2-pyridinesulfonyl chloride (Formula UUU-4) Refer to Chart UUU

To a suspension of 1.27 g of the title compound of Preparation 140 in 25 mL of 1N aqueous hydrochloric acid and 5 mL of acetic acid at 0° C. is vigorously bubbled in chlorine gas. After 15 minutes, the chlorine gas addition is

ceased and replaced with nitrogen gas. The resulting solid is collected and washed sequentially with cold dilute aqueous hydrochloric acid and water. The solid is dried in vacuo to afford 1.60 g of the title product as a tan solid.

Physical characteristics are as follows:

MP 77°–80° C.

^{1}H NMR ($CDCl_3$) δ8.3, 8.8, 9.6 ppm

PREPARATION 142

N-[3-(1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-5-nitro-2-pyridinesulfonamide (Formula UUU-5: R_1 is 2-phenylethyl, R_2 is propyl, R_3 is tert-butyl) Refer to Chart UUU

To a solution of 210 mg of the title compound of Preparation 81 (Formula T-4) in 2 mL of dichloromethane at 0° C. is added 80 μL of pyridine followed by 111 mg of the title compound of Preparation 141 (Formula UUU-4). After warming to room temperature overnight, the reaction mixture is column chromatographed on flash silica gel eluting with 3% to 9% ethyl acetate in dichloromethane to provide 303 mg of the title compound as a yellow foam.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$—CD_3OD) δ0.8–1.0, 1.2–1.4, 1.6–1.9, 2.4–2.7, 4.0, 6.9–7.4, 8.0, 8.5, 9.4 ppm

HRMS 608.2412 (EI)

EXAMPLE 299

5-Amino-N-[3-(1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl) phenyl]-2-pyridinesulfonamide (Formula UUU-6: R_1 is 2-phenylethyl, R_2 is propyl, R_3 is tert-butyl) Refer to Chart UUU

To a solution of 300 mg of the title compound of Preparation 142 (Formula UUU-5) in 5 mL of methanol under argon is added 500 mg of ammonium formate followed by 100 mg of 10% palladium on carbon. After 1 hour, the reaction mixture is filtered through a pad of Celite with methanol washes. The combined filtrates are concentrated under reduced pressure and the residue is repeatedly triturated with portions of dichloromethane. The combined dichloromethane washes are concentrated under reduced pressure and the residue is column chromatographed on flash silica gel eluting with 50% ethyl acetate in dichloromethane to provide 246 mg of the title compound as a white solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$—CD_3OD) δ0.8–1.0, 1.2–1.4, 1.5–2.0, 2.4–2.6, 4.0, 6.7, 6.8–7.3, 7.4, 7.9 ppm

HRMS 577.2617 (EI)

EXAMPLE 300–327

Following the procedures and preparations described above and using starting materials known and available to one of ordinary skill in organic synthesis, the following additional compounds in Table 3 of the present invention are made from the compounds prepared in the following preparations:

PREPARATION 143

Preparative separation of N-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl-carbamic acid phenylmethyl ester, to give 4 isomers

The title compound of Preparation 134 is separated into four constituent steroisomers which are (in order of elution from system A) 4 isomers: Isomer 1, Isomer 2, Isomer 3, and Isomer 4 with the following approximate observed retention times 10.5, 14.9, 21.4 and 65.2 minutes respectively. System A consists of a 0.46×25 cm Chiralcel OD-H column eluting at 0.5 mL/min with 20% isopropanol and 0.1% trifluoracetic acid in hexane (V/V). (Chiralcel OD-H is a registered trademark of Chiral Technologies, Inc., Exton Pa. 19341.)

The first phase of the separation is accomplished with a 2.1×25 cm (R,R)Whelk-O 1 column eluting with 20% (V/V) isopropanol in hexane at 12 mL/min. ((R,R)Whelk-O 1 is a registered trademark of Regis Technologies, Inc., Morton Grove, Ill. 60053.) The peaks eluting at approximately 35 and 41 min are, respectively, a mixture of Isomers 3 and 4 and a mixture of Isomers 1 and 2 as judged from System A, above. The two mixtures are further treated as below.

In the second phase of the separation, the mixture from above that elutes near 41 minutes is injected onto a 2.1×25 cm Chiralcel OD column (Chiral Technologies, Inc.) and eluting with 15% isopropanol and 0.05% trifluoracetic acid in hexane (V/V) at 9.0 mL/min. The peaks that elute near 11.0 and 22.0 minutes are, respectively, Isomer 1 and Isomer 2 as judged from System A.

In the final phase of the separation, the mixture that elutes from the (R,R)Whelk-O 1 column near 35 minutes is injected onto a 2.2×25 cm Chiralcel OD column eluting with 35% isopropanol and 0.1% trifluoroacetic acid (V/V) in hexane at 9.0 mL/min. The isomer that elutes near 9.7 minutes is Isomer 3 and the one that elutes near 16.6 minutes is Isomer 4.

In both phases of the separation of stereoisomers, fractions are pooled after assay with System A and pools are concentrated to dryness on a rotary evaporator.

PREPARATION 144

Resolution of N-[3-(1-[5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]carbamic acid, phenylmethyl ester to give 2 isomers

Samples of the starting compound (up to 1.0 gm each run) are injected onto a 5.1×50 cm Chiralcel OD column (Chiral Technologies, Inc.). The enantiomers elute at about 23 min (This corresponds to the benzyloxycarbonyl protected analogue of amine (Isomer 1) (EI-MS: 359 [M+]; ^{1}H NMR ($CDCl_3$—CD_3OD): 7.1–6.9, 6.5, 4.2, 2.6–2.3, 1.8–1.2, 1.1, 0.9; TLC: R_f=0.42 (10% ethyl acetate in dichloromethane)), and at about 33 min (This corresponds to the benzyloxycarbonyl protected analogue of amine (Isomer 2) (EI-MS: 359 [M+]; ^{1}H NMR ($CDCl_3$—CD_3OD): 7.1–6.9, 6.5, 4.2, 2.6–2.3, 1.8–1.2, 1.1, 0.9; TLC: R_f=0.42 (10% ethyl acetate in dichloromethane)). The mobile phase is 20% isopropanol and 0.1% acetic acid in hexane (V/V) pumped at 60 mL/min. The purity is checked on a 0.46×25 cm Chiralcel OD-H column (Chiral Technologies, Inc.). The mobile phase is 20% isopropanol in hexane (V/V) and 0.05% trifluoroacetic acid pumped at 0.5 mL/min. The observed retention times are 8.9 and 16.7 min (monitor set at 238 nm) for Isomer 1 and Isomer 2, respectively.

PREPARATION 145

Resolution of N-[3-(1-[6,6-Bis(2-phenylethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]carbamic acid, phenylmethyl ester to give 2 isomers

Samples of the starting compound (up to 1.3 gm each run) are injected onto a 5.1×50 cm Chiralcel OD column (Chiral Technologies, Inc.). The enantiomers are eluted with 20% isopropanol and 0.025% acetic acid in hexane (V/V) at 60 mL/min until the first enantiomer elutes. At this point (approximately 120 min into the run) the flow rate is increased to 90 mL/min to expedite elution of the second enantiomer. The enantiomers elute near 91.2 min (This is the

corresponding benzyloxycarbonyl analogue of amine Isomer 1 and near 132 min (This is the corresponding benzyloxycarbonyl analogue of amine Isomer 2. The purity is checked on a 0.46×25 cm Chiralcel OD-H column. The mobile phase is 30% isopropanol in hexane (V/V) pumped at 0.5 mL/min.

PREPARATION 146

5-Carbamoylpyridine-2-sulfonyl chloride (Formula VVV-2) Refer to Chart VVV

Into a cold (0°), stirred suspension of 400 mg of 2-mercapto-5-carbamoylpyridine of formula VVV-1 in 7.5 ml of 1N HCl is passed a brisk stream of chlorine gas. After ten minutes, the suspension is filtered, and the solid washed well with water and dried in vacuo. Obtained is 517 mg of the title compound as a nearly white solid.

EXAMPLE 328

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-4-cyanobenzenesulfonamide (Formula U-8: R_1 is tert-butyl, R_2 is 4-cyanophenyl) Refer to Chart U

Using the general sulfonation procedure of Example 252, 88 mg of the amine of Preparation 86 (Formula U-7, R_1 is tert-butyl) is reacted with 4-cyanobenzenesulfonyl chloride. Flash chromatography on silica gel using 10% ethyl acetate in dichloromethane provides 117 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.90, 1.3, 1.7, 2.5, 3.6, 6.8–7.4, 7.6, 7.8 ppm

HRMS: 605.2478

R_f 0.36 (10% ethyl acetate in dichloromethane)

EXAMPLE 329

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-8-quinolinesulfonamide (Formula U-8: R_1 is tert-butyl, R_2 is 8-quinolyl) Refer to Chart U

Using the general sulfonylation procedure of Example 252, 88 mg of the amine of Preparation 86 (Formula U-7, R_1 is tert-butyl) is reacted with 8-quinolinesulfonyl chloride. Flash chromatography on silica gel using 5–10% ethyl acetate in dichloromethane provides 101 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.63, 0.9, 1.1, 1.3, 1.6–1.9, 2.4–2.6, 6.7–7.6, 8.0, 8.2, 9.1 ppm

HRMS: 631.2638

R_f 0.30 (5% ethyl acetate in dichloromethane)

EXAMPLE 330

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 1-methylimidazole-4-yl) Refer to Chart D

Using the general sulfonylation procedure of Example 252, 77 mg of the amine of Formula D-5, wherein R_1 and R_2 are phenethyl and R_3 is ethyl, is reacted with 1-methylimidazole-4-sulfonyl chloride. Flash chromatography on silica gel using 3% methanol in dichloromethane provides 97.0 mg of the title compound as a crystalline white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.88, 1.9–2.2, 2.6, 3.6–3.8, 3.97, 6.9–7.5 ppm

HRMS: 600.2521

R_f 0.31 (5% methanol in dichloromethane)

EXAMPLE 331

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula D-6: R_1 is phenethyl, R_2 is phenethyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) Refer to Chart D

Using the general sulfonylation procedure of Example 252, 77 mg of the amine of Formula D-5, wherein R_1 and R_2 phenethyl and R_3 is ethyl,is reacted with 5-cyanopyridine-2-sulfonyl chloride. Flash chromatography on silica gel using 10% ethyl acetate in dichloromethane provides 88.3 mg of the title compound as a crystalline white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.85, 1.8–2.2, 2.5–2.7, 3.97, 6.9–7.4, 7.9, 8.8 ppm.

HRMS: 622.2355

R_f 0.28 (10% ethyl acetate in dichloromethane)

EXAMPLE 332

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-carbamoylpyridine-2-sulfonamide (Formula U-8: R_1 is ethyl, R_2 is 5-carbamoylpyridine-2-yl) Refer to Chart U

Using the general sulfonylation procedure of Example 252, 82 mg of the amine of Formula U-7, wherein R_1 is ethyl, is reacted with 5-carbamoylpyridine-2-sulfonyl chloride of Preparation 146. Flash chromatography on silica gel using 3–6% methanol in dichloromethane provides 55.4 mg of the title compound as an amorphous solid.

Physical characteristics are as follows:

^{1}H NMR δ0.7–0.9, 1.3, 1.6–2.1, 2.5, 3.9, 6.8–7.3, 7.8, 8.2 ppm.

HRMS: 596.2216

R_f 0.16 (5% methanol in dichloromethane)

EXAMPLE 333

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)propyl}phenyl]-5-carbamoylpyridine-2-sulfonamide (Formula V-8: R_1 is ethyl, R_2 is 5-carbamoylpyridine-2-yl) Refer to Chart V

Using the general sulfonylation procedure of Example 252, 98 mg of the amine of formula V-7, wherein R_1 is ethyl) is reacted with 5-carbamoylpyridine-2-sulfonyl chloride of Preparation 146. Flash chromatography on silica using 3–6% methanol in dichloromethane provides 58.3 mg of the title compound as an amorphous solid.

Physical characteristics are as follows:

^{1}H NMR δ0.83, 1.8–2.2, 2.5–2.6, 6.8–7.2, 7.8, 8.1, 9.0 ppm.

HRMS: 676.2297

R_f 0.17 (5% methanol in dichloromethane)

EXAMPLE 334

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl}phenyl]-5-carbamoylpyridine-2-sulfonamide (Formula D-6: R_1 is propyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-carbamoylpyridine-2-yl) Refer to Chart D

Using the general sulfonylation procedure of Example 252, 66 mg of the amine of Formula D-5 (R_1 and R_2 are propyl, R_3 is ethyl) is coupled with 5-carbamoylpyridine-2-sulfonyl chloride of Preparation 146 to yield, after flash chromatography on silica gel using 3–6% methanol in dichloromethane, 83.8 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.7–0.9, 1.2–2.1, 3.87, 7.0–7.3, 7.8, 8.2 ppm.

HRMS: 516.2156

R_f 0.22 (5% methanol in dichloromethane)

PREPARATION 147

Resolution of N-[3-[1-(4-Hydroxy-5,6-dihydro-2-oxo-6-phenethyl-6-propyl-2H-pyran-3-yl)propyl]phenyl]-carbamic acid, phenylmethyl ester to give 4 isomers (Formula WWW-2: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl) Refer to Chart WWW and RRR

The four isomers of the product of Preparation 130A (Formula RRR-1; R_1=ethyl) are (in order of increasing retention time on System B): (ca. 16.9 min) (Isomer 1), (ca. 28.0 min) (Isomer 2), (ca. 38.2 min) (Isomer 3) and (ca. 49.8 min) (Isomer 4). System B consists of a 0.46×25 cm Chiralcel OD-H column (Chiral Technologies, Inc.) eluting with 25% isopropanol in hexane (V/V) at 0.5 mL/min.

In Phase one of the complete resolution repeatedly inject 55 mg samples of the product of Preparation 130A onto a 2.1×25 cm (R,R)Whelk-O 1 column (Regis Technologies, Inc.). Elute the isomers at 10 mL/min with 35% isopropanol and 0.5% acetic acid in hexane (V/V). The first of the three peaks to elute (near 12 min) is a mixture of Isomers 1 (Formula RRR-4 of Chart RRR) and 2 (Formula RRR-3 of Chart RRR) as shown by injecting aliquots in System B. Resolve this mixture in Phase 2, below.

The second phase consists of a 2.1×25 cm Chiralcel OD column kept at 30°. Inject 60 mg batches of the mixture obtained in the first phase and elute the enantiomers with 25% isopropanol and 0.05% trifluoroacetic acid (V/V) at 9 mL/min. Separately pooled and concentrated, the fractions eluting near 14.5 and 23.9 min to give Isomers 1 (Formula RRR-4 where R_1 is ethyl of Chart RRR) and 2 (formula RRR-3 where R_1 is ethyl of Chart RRR) respectively.

PREPARATION 147A

3-(R or S)-[1-(3-aminophenyl)-propyl]-4-hydroxy-5,6-dihydro-6-(R or S)-phenethyl-6-(R or S)-propyl-2H-pyran-2-one (Formula RRR-7; R_1 is ethyl; Refer to Chart RRR)

Following the procedure of Preparation 132 beginning with the peak identified as peak 2 (Formula RRR-3; R_1 is ethyl of Chart RRR) from the chiral resolution of the product of Preparation 147, the title compound is prepared.

Physical characteristics are as follows:

^{1}H NMR (CD_3OD): δ6.5–7.3, 3.9–4.0, 2.5–2.7, 1.2–2.3, 0.8–1.0.

TLC (silica gel GF): Rf=0.31, 40% ethyl acetate in hexane.

EXAMPLE 335

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 1] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is phenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the first stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 147. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–1.0, 1.2–2.6, 3.3–3.6, 6.9–7.3, 7.7–8.2, 8.8–9.0 ppm.

HRMS: 560.2210

R_f 0.41 (15% ethyl acetate in dichloromethane)

EXAMPLE 336

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 2] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine that is the title product of Preparation 147A (Formula WWW-3, where R_1 is phenethyl, R_2 is propyl, and R_3 is ethyl). The amine is derived from the second stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 147A. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.6–2.6, 3.3–3.6, 6.9–7.3, 7.7–8.2, 8.8–9.0 ppm.

HRMS: 560.2215

R_f 0.41 (15% ethyl acetate in dichloromethane)

EXAMPLE 337

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 3] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is phenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the third stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 147. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.6–2.6, 3.3–3.6, 6.9–7.3, 7.7–8.2, 8.8–9.0 ppm.

HRMS: 560.2210

R_f 0.41 (15% ethyl acetate in dichloromethane)

EXAMPLE 338

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 4] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is phenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the fourth stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 147. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–1.0, 1.2–2.6, 3.3–3.6, 6.9–7.3, 7.7–8.2, 8.8–9.0 ppm.

HRMS: 560.2210

R_f 0.41 (15% ethyl acetate in dichloromethane)

EXAMPLE 339

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) [Isomer 1] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is phenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the first stereoisomer

of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 147. The title compound is obtained as an amorphous solid after flash chromatography on silica using 3% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–2.8, 3.2–3.7, 3.9, 7.0–7.6 ppm.

HRMS: 537.2317

R_f 0.36 (5% methanol in dichloromethane)

EXAMPLE 340

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-phenethyl- 6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) [Isomer 2] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is phenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the second stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 147. The title compound is obtained as an amorphous solid after flash chromatography on silica using 3–4% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–2.7, 3.3–3.7, 4.0, 7.0–7.5 ppm.

HRMS: 537.2275

R_f 0.36 (5% methanol in dichloromethane)

EXAMPLE 341

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) [Isomer 3] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is phenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the third stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 147. The title compound is obtained as an amorphous solid after flash chromatography on silica using 3% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–2.7, 3.3–3.7, 4.0, 7.0–7.5 ppm.

HRMS: 537.2329

R_f 0.36 (5% methanol in dichloromethane)

EXAMPLE 342

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4: R_1 is phenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) [Isomer 4] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is phenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the fourth stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 147. The title compound is obtained as an amorphous solid after flash chromatography on silica using 3% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–2.8, 3.2–3.7, 3.9, 7.0–7.6 ppm.

HRMS: 537.2312

R_f 0.36 (5% methanol in dichloromethane)

PREPARATION 148

3-[(3-Nitrophenyl)methyl]-6,6-diphenethyl-4-hydroxy-5,6-dihydro-2H-pyran-2-one (Formula XXX-3) Refer to Chart XXX

To a solution of 172 mg of 6,6-Diphenethyl-4-hydroxy-5,6-dihydro-2H-pyran-2-one of formula XXX-1 and 81 mg of meta-nitrobenzaldehyde in 2 ml of dry THF, under argon, is added a solution of 142 mg of $AlCl_3$ in 1 ml of THF. The solution is stirred at room temperature for 2 hours, then quenched with 310 mg of sodium carbonate decahydrate, diluted with ether, and filtered through Celite with ether rinses. Following removal of solvent under reduced pressure, 264 mg of crude benzylidene of Formula XXX-2 is obtained. This material is dissolved in 5 ml of methanol, and the solution cooled to 0° for the addition of 44 mg of sodium cyanoborohydride. After an hour, a further 20 mg aliquot of sodium cyanoborohydride is added. After another 30 minutes, the mixture is acidified with dilute HCl to pH 1 and extracted with three portions of dichloromethane. The extract is dried ($MgSO_4$) and then concentrated under reduced pressure. Flash chromatography of the residue on silica using 5–20% ethyl acetate in dichloromethane provides 211 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ2.0, 2.7, 3.8, 7.0–7.4, 7.6, 8.0, 8.2 ppm.

MS: M+ 457

R_f 0.25 (5% ethyl acetate in dichloromethane)

PREPARATION 149

3-[(3-Aminophenyl)methyl]-6,6-diphenethyl-4-hydroxy-5,6-dihydro-2H-pyran-2-one (Formula XXX-4) Refer to Chart XXX

A mixture of 211 mg of the product of Preparation 148 (Formula XXX-3) and 50 mg of 10% palladium on carbon in 5 ml of methanol is stirred at room temperature under 1 atmosphere hydrogen gas. After two hours, the mixture is filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue on silica using 25% ethyl acetate in dichloromethane affords 133.6 mg of the title compound.

Physical characteristics are as follows:

^{1}H NMR δ2.0, 2.6, 3.6, 4.1, 6.5, 6.6, 6.7, 6.9–7.3 ppm.

MS: M+ 427

R_f 0.33 (25% ethyl acetate in dichloromethane)

EXAMPLE 343

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula YYY-5) R_1 and R_2 are phenethyl, R_3 is 1-methylimidazole-4-yl) Refer to Chart YYY

Using the general sulfonylation procedure of Example 252, 77 mg of the amine of formula YYY-4 (R_1 and R_2 are phenethyl) is reacted with 1-methylimidazole-4-sulfonyl chloride. Flash chromatography on silica using 3% methanol in dichloromethane provides 90.7 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.96, 1.0, 1.6–2.7, 3.45, 6.8–7.5 ppm.

HRMS: 628.2832

R_f 0.38 (3% methanol in dichloromethane)

EXAMPLE 344

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula YYY-5) R_1 and R_2 are phenethyl, R_3 is 5-cyanopyridine-2-yl) Refer to Chart YYY

Using the general sulfonylation procedure of Example 252, 77 mg of the amine of Formula YYY-4 (R_1 and R_2 are phenethyl) is reacted with 5-cyanopyridine-2-sulfonyl chlo-

ride. Flash chromatography on silica using 10% ethyl acetate in dichloromethane provides 86.1 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.96, 1.8–2.2, 2.5–2.8, 4.1, 4.3, 6.9–7.4, 7.9–8.0, 8.9 ppm.

HRMS: 650.2681

R_f 0.27 (10% ethyl acetate in dichloromethane)

PREPARATION 150

Resolution of N-[3-[1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]carbamic acid, phenylmethyl ester to give 4 isomers (Formula WWW-2: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is t-butyl) Refer to Chart WWW

System C is used to track the enantiomers and to monitor the preparative columns. System C consists of a 0.46×25 cm Chiralcel OD-H column (Chiral Technologies, Inc.) with 15% isopropanol in hexane (V/V) at 0.5 mL/min. The peaks eluting near 13.5, 18.8, 37.1 and 79.7 min are, respectively, Isomer 1, Isomer 2, Isomer 3, and Isomer 4.

Separate Isomers 3 and 4 from the mixture on a 2.1×25 cm (R,R)Whelk-O 1 column (Regis Technologies, Inc.). These two isomers elute at about 23.9 and 26.8 min when the column is developed with 20% isopropanol in hexane (V/V) at 10 mL/min at 30°. The desired isomers elute as an unresolved mixture near 28.9 min and are separated in the second stage of the resolution.

For the second stage inject the unresolved mixture onto a 2.1×25 cm Chiralcel OD column (Chiral technologies, Inc.) kept at 30°. With 12% isopropanol in hexane (V/V) at 12 mL/min, Isomer 1 emerges near 14.5 min and Isomer 2 emerges near 20.8 min.

EXAMPLE 345

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 1] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is 4-fluorophenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the first stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 150. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–2.7, 3.2, 3.5, 3.6, 3.7, 4.1, 6.8–7.4, 7.5, 7.8–8.2, 8.8 ppm.

HRMS: 606.2429

R_f 0.40 (15% ethyl acetate in dichloromethane)

EXAMPLE 346

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 2] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is 4-fluorophenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the second stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 150. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.6, 0.7–2.6, 3.4, 3.5, 3.7, 4.2, 6.8–7.3, 7.5, 7.8–8.2, 8.8–9.0 ppm.

MS: 606.2434

R_f 0.40 (15% ethyl acetate in dichloromethane)

EXAMPLE 347

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethyl-propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 3] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is 4-fluorophenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the third stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 150. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.6, 0.7–2.6, 3.4, 3.5, 3.7, 4.2, 6.8–7.3, 7.5, 7.8–8.2, 8.8–9.0 ppm.

MS: 606.2423

R_f 0.40 (15% ethyl acetate in dichloromethane)

EXAMPLE 348

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 5-cyanopyridine- 2-yl) [Isomer 4] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is 4-fluorophenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the fourth stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 150. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–2.7, 3.2, 3.5, 3.6, 3.7, 4.1, 6.8–7.4, 7.5, 7.8–8.2, 8.8 ppm.

HRMS: 606.2429

R_f 0.40 (15% ethyl acetate in dichloromethane)

EXAMPLE 349

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 1-methylimidazol-4-yl [Isomer 1] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is 4-fluorophenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the first stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 150. The title

compound is obtained as an amorphous solid after flash chromatography on silica using 3% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.4, 1.7, 2.3–2.7, 3.6, 3.9, 4.1, 6.8–7.5 ppm.

HRMS: 584.2585

R_f 0.34 (5% methanol in dichloromethane)

EXAMPLE 350

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 1-methylimidazol-4-yl [Isomer 2] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is 4-fluorophenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the second stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 150. The title compound is obtained as an amorphous solid after flash chromatography on silica using 3% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–1.1, 1.3, 1.7, 2.3–2.7, 3.6, 3.9, 4.1, 6.8–7.5 ppm.

HRMS: 584.2585

R_f 0.34 (5% methanol in dichloromethane)

EXAMPLE 351

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 1-methylimidazol-4-yl [Isomer 3] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is 4-fluorophenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the third stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 150. The title compound is obtained as an amorphous solid after flash chromatography on silica using 3% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.7–1.1, 1.3, 1.7, 2.3–2.7, 3.6, 3.9, 4.1, 6.8–7.5 ppm.

HRMS: 584.2591

R_f 0.34 (5% methanol in dichloromethane)

EXAMPLE 352

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is tert-butyl, R_4 is 1-methylimidazol-4-yl [Isomer 4] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 is 4-fluorophenethyl, R_2 is propyl, and R_3 is ethyl. The amine is derived from the fourth stereoisomer of Formula WWW-2 to elute from a Chiralcel OD chiral HPLC column of Preparation 150. The title compound is obtained as an amorphous solid after flash chromatography on silica using 3% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.4, 1.7, 2.3–2.7, 3.6, 3.9, 4.1, 6.8–7.5 ppm.

HRMS: 584.2580

R_f 0.34 (5% methanol in dichloromethane)

EXAMPLE 353

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)methyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula XXX-5, R_1 is 5-cyanopyridine-2-yl) Refer to Chart XXX

Using the general sulfonylation procedure of Example 252, 64 mg of the amine of formula XXX-4 is reacted with 5-cyanopyridine-2-sulfonyl chloride. Flash chromatography on silica using 2–3% methanol in dichloromethane provides 73.2 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ1.8–2.1, 2.6, 6.9–7.3, 7.9, 8.8 ppm.

HRMS: 594.2068

R_f 0.40 (3% methanol in dichloromethane)

EXAMPLE 354

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)methyl}phenyl]-5-aminopyridine-2-sulfonamide (Formula UUU-6, R_1 and R_2 are phenethyl, R_3 is H). Refer to Chart UUU

Using the general sulfonylation procedure of Example 252, 69 mg of the amine of formula XXX-4 is reacted with 5-nitropyridine-2-sulfonyl chloride. Flash chromatography on silica using 2-3% methanol in dichloromethane provides 107 mg of the intermediate nitro compound of formula UUU-5 (R_1 and R_2 are phenethyl, R_3 is H). Reduction to the amine is accomplished using hydrogen gas and palladium on carbon catalyst. Flash chromatography on silica gel using 4–6% methanol in dichloromethane provides 65.0 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ1.9–2.1, 2.6, 3.5–4.0, 6.7, 6.9–7.3, 7.5, 7.9 ppm.

HRMS: 584.2215

R_f 0.24 (5% methanol in dichloromethane)

PREPARATION 151

Resolution of N-[3-[1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]carbamic acid, phenylmethyl ester to give 2 enantiomers (Formula WWW-2: R_1 and R_2 are phenethyl, R_3 is t-butyl) Refer to Chart WWW

Inject 40 mg batches of the starting compound onto a 2.1×25 cm (R,R)Whelk-O 1 column (Regis Technologies, Inc.) that is maintained at 30°. The 2 enantiomers elute at about 37 min (Enantiomer 1) and 43 min (Enantiomer 2) using 25% isopropanol and 0.05% acetic acid at 12 mL/min. Fractions are pooled on the basis of results from analysis on a 0.46×25 cm (R,R)Whelk-O 1 column eluted with 30% isopropanol and 0.1% acetic acid (V/V) at 1.0 mL/min. The isomers elute at (Isomer 1) 19.1 and (Isomer 2) 23.0 min respectively.

EXAMPLE 355

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-aminopyridine-2-sulfonamide (Formula WWW-4, R_1 and R_2 are phenethyl, R_3 is tert-butyl, R_4 is 5-aminopyridine-2-yl) [Enantiomer 1] Refer to Chart WWW

Using the general sulfonylation procedure of Example 252, 73 mg of the amine of Formula WWW-3 (R_1 and R_2 are phenethyl, R_3 is tert-butyl) is reacted with 5-nitropyridine-

2-sulfonyl chloride. The amine used is derived from the first enantiomer of Formula WWW-2 to elute from an (R,R) Whelk-O chiral HPLC column of Preparation 151. Flash chromatography on silica using 5–10% ethyl acetate in dichloromethane provides 94.0 mg of the intermediate nitro compound of formula UUU-5 (R_1 and R_2 are phenethyl, R_3 is tert-butyl). Reduction to the amine is accomplished using hydrogen gas and palladium on carbon catalyst. Flash chromatography on silica gel using 4% methanol in dichloromethane provides 74.8 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.95, 2.0, 2.6, 6.8, 6.9–7.4, 7.5, 7.9 ppm.

HRMS: 640.2828

R_f 0.27 (5% methanol in dichloromethane)

EXAMPLE 356

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-aminopyridine-2-sulfonamide (Formula WWW-4, R_1 and R_2 are phenethyl, R_3 is tert-butyl, R_4 is 5-aminopyridine-2-yl) [Enantiomer 2] Refer to Chart WWW

Using the general sulfonylation procedure of Example 252, 73 mg of the amine of Formula WWW-3 (R_1 and R_2 are phenethyl, R_3 is tert-butyl) is reacted with 5-nitropyridine-2-sulfonyl chloride. The amine used is derived from the second enantiomer of Formula WWW-2 to elute from an (R,R)Whelk-O chiral HPLC column of Preparation 151. Flash chromatography on silica using 5–10% ethyl acetate in dichloromethane provides 91.3 mg of the intermediate nitro compound of formula UUU-5 (R_1 and R_2 are phenethyl, R_3 is tert-butyl). Reduction to the amine is accomplished using hydrogen gas and palladium on carbon catalyst. Flash chromatography on silica gel using 4% methanol in dichloromethane provides 54.3 mg of the title compound as an amorphous white solid.

Physical characteristics are as follows:

^{1}H NMR δ0.95, 2.0, 2.6, 6.8, 6.9–7.4, 7.5, 7.9 ppm.

HRMS: 640.2828

R_f 0.27 (5% methanol in dichloromethane)

EXAMPLE 357

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4, R_1 and R_2 are phenethyl, R_3 is tert-butyl, R_4 is 1-methylimidazol-4-yl) [Enantiomer 1] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 and R_2 are phenethyl and R_3 is tert-butyl. The amine is derived from the first enantiomer of Formula WWW-2 to elute from an (R,R)Whelk-O chiral HPLC column of Preparation 151. The title compound is obtained as an amorphous solid after flash chromatography on silica using 3% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.98, 2.0, 2.6, 3.6, 3.8, 6.9–7.5 ppm.

HRMS: 628.2832

R_f 0.38 (5% methanol in dichloromethane)

EXAMPLE 358

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4, R_1 and R_2 are phenethyl, R_3 is tert-butyl, R_4 is 1-methylimidazol-4-yl) [Enantiomer 2] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 and R_2 are phenethyl and R_3 is tert-butyl. The amine is derived from the second enantiomer of Formula WWW-2 to elute from an (R,R)Whelk-O chiral HPLC column of Preparation 151. The title compound is obtained as an amorphous solid after flash chromatography on silica using 3% methanol in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.98, 2.0, 2.6, 3.6, 3.8, 6.9–7.5 ppm.

HRMS: 628.2838

R_f 0.38 (5% methanol in dichloromethane)

EXAMPLE 359

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4, R_1 and R_2 are phenethyl, R_3 is tert-butyl, R_4 is 5-cyanopyridine-2-yl) [Enantiomer 1] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 and R_2 are phenethyl and R_3 is tert-butyl. The amine is derived from the first enantiomer of Formula WWW-2 to elute from an (R,R)Whelk-O chiral HPLC column of Preparation 151. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.87, 1.9, 2.6, 6.8–7.4, 7.9, 8.8 ppm.

HRMS: 650.2681

R_f 0.46 (15% ethyl acetate in dichloromethane)

EXAMPLE 360

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4, R_1 and R_2 are phenethyl, R_3 is tert-butyl, R_4 is 5-cyanopyridine-2-yl) [Enantiomer 2] Refer to Chart WWW

The title compound is prepared using the general sulfonylation procedure of Example 252, using the amine of Formula WWW-3, where R_1 and R_2 are phenethyl and R_3 is tert-butyl. The amine is derived from the second enantiomer of Formula WWW-2 to elute from an (R,R)Whelk-O chiral HPLC column of Preparation 151. The title compound is obtained as an amorphous solid after flash chromatography on silica using 10% ethyl acetate in dichloromethane.

Physical characteristics are as follows:

^{1}H NMR δ0.87, 1.9, 2.6, 6.8–7.4, 7.9, 8.8 ppm.

HRMS: 650.2681

R_f 0.46 (15% ethyl acetate in dichloromethane)

PREPARATION 152

Resolution of N-[3-[1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl]phenyl]carbamic acid, phenylmethyl ester to give 2 isomers (Formula WWW-2: R_1 and R_2 are propyl, R_3 is ethyl) Refer to Chart WWW

Samples of the starting compound are injected onto a 2.1×25 cm Chiralcel OD column and eluted with 20% isopropanol (V/V) in hexane at 10 mL/min. The material eluting near 19.1 minutes is one isomer (Enantiomer 1) and that eluting near 37.7 minutes is another isomer (Enantiomer 2). The pools are concentrated separately on a rotary evaporator (ca. 30 mm, bath at 50° maximum) to give white solids.

EXAMPLE 361

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4, R_1 and R_2 are propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Enantiomer 1] Refer to Chart WWW

Following procedures analogous to those described above, but using Enantiomer 1 of Preparation 152, the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.2–2.2, 3.90, 6.9–7.2, 8.0, 8.15, 8.9 ppm.

HRMS: 497.1984

R_f 0.38 (15% ethyl acetate in dichloromethane)

EXAMPLE 362

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4, R_1 and R_2 are propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Enantiomer 2] Refer to Chart WWW

Following procedures analogous to those described above, but using Enantiomer 2 of Preparation 152, the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.2–2.2, 3.90, 6.9–7.2, 8.0, 8.15, 8.9 ppm.

HRMS: 497.1980

R_f 0.38 (15% ethyl acetate in dichloromethane)

EXAMPLE 363

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-aminopyridine-2-sulfonamide (Formula WWW-4, R_1 and R_2 are propyl, R_3 is ethyl, R_4 is 5-aminopyridine-2-yl) [Enantiomer 1] Refer to Chart WWW

Following procedures analogous to those described above, but using Enantiomer 1 of Preparation 152, the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR δ0.7–0.9, 1.2–2.2, 3.8, 6.8–7.2, 7.5, 7.9 ppm.

HRMS: 487.2122

R_f 0.28 (5% methanol in dichloromethane)

EXAMPLE 364

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-aminopyridine-2-sulfonamide (Formula WWW-4, R_1 and R_2 are propyl, R_3 is ethyl, R_4 is 5-aminopyridine-2-yl) [Enantiomer 2] Refer to Chart WWW

Following procedures analogous to those described above, but using Enantiomer 2 of Preparation 152, the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR δ0.7–0.9, 1.2–2.2, 3.8, 6.8–7.2, 7.5, 7.9 ppm.

HRMS: 487.2140

R_f 0.28 (5% methanol in dichloromethane)

PREPARATION 153

Resolution of N-[3-[1-(4-Hydroxy-5,6-dihydro-2-oxo-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl]-phenyl]carbamic acid, phenylmethyl ester to give 4 isomers (Formula WWW-2: R_1 is 4-fluorophenethyl, R_2 is propyl, and R_3 is ethyl) Refer to Chart WWW

The enantiomers are defined by elution order from System D. HPLC System D consists of a 0.46×25 cm Chiralcel OD-H column (Chiral Technologies, Inc.) with 20% isopropanol and 0.05% trifluoroacetic acid in hexane (V/V) pumped at 0.5 mL/min. The retention times in this system are (Isomer 1) 21.6, (Isomer 2) 34.5, (Isomer 3) 55.2 and (Isomer 4) 66.6 min.

Separate the enantiomers on a 2.1×25 cm Chiralcel OD column (Chiral Technologies, Inc.). Aliquots are injected and the enantiomers eluted with 17.5% isopropanol in hexane (V/V) at 10 mL/min. Fractions eluting near 24.6, 42.9, 66.3 and 77.4 min are pooled appropriately after assay with System D. In order of elution, the four isomers are designated Isomers 1–4, respectively.

In all cases, whenever solvent is stripped from a pool the following protocol is used: Solvent is removed from pools of fractions on a rotary evaporator with house vacuum (ca. 30 mm Hg) and a water bath set at 45°±5°. If acetic acid is present in the solvent, add ca. 10 mL of toluene/L of pool before the flask goes dry. Residues are then washed into tared flasks using methylene chloride and the solvent is stripped as above. Final solvent removal is accomplished at ambient temperature, 1 mmHg pressure for 2–24 hours before weighing.

EXAMPLE 365

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl) propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 1] Refer to Chart WWW

Following procedures analogous to those described above, but using Isomer 1 of Preparation 153, the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.3, 1.6–2.2, 2.5, 3.9, 6.8–7.3, 7.9–8.1, 8.9 ppm.

HRMS: 578.2120

R_f 0.35 (15% ethyl acetate in dichloromethane)

EXAMPLE 366

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl) propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 2] Refer to Chart WWW

Following procedures analogous to those described above, but using Isomer 2 of Preparation 153, the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.3, 1.6–2.2, 2.5, 3.9, 6.8–7.3, 7.9–8.1, 8.9 ppm.

HRMS: 578.2120

R_f 0.35 (15% ethyl acetate in dichloromethane)

EXAMPLE 367

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl) propyl}phenyl]-5-cyanopyridine-2-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 3] Refer to Chart WWW

Following procedures analogous to those described above, but using Isomer 3 of Preparation 153, the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.3, 1.6–2.2, 2.5, 3.9, 6.8–7.3, 7.9–8.1, 8.9 ppm.

HRMS: 578.2126

R_f 0.35 (15% ethyl acetate in dichloromethane)

EXAMPLE 367A

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S or R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl) propyl}phenyl]-5-cyanopyridine- 2-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-cyanopyridine-2-yl) [Isomer 4] Refer to Chart WWW

Following procedures analogous to those described above, but using Isomer 4 of Preparation 153, the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.3, 1.6–2.2, 2.5, 3.9, 6.8–7.3, 7.9–8.1, 8.9 ppm.

HRMS: 578.2126

R_f 0.35 (15% ethyl acetate in dichloromethane)

EXAMPLE 368

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl) propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 1-methylimidazol-4-yl) [Isomer 1] Refer to Chart WWW

Following procedures analogous to those described above, but using Isomer 1 of Preparation 153, the title compound are as follows:

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.3, 1.6–2.2, 2.6, 3.63, 4.0, 6.9–7.5 ppm.

HRMS: 556.2265

R_f 0.29 (5% methanol in dichloromethane)

EXAMPLE 369

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl) propyl}phenyl]-5-aminopyridine-2-sulfonamide (Formula WWW-4: R_1 is 4-fluorophenethyl, R_2 is propyl, R_3 is ethyl, R_4 is 5-aminopyridine-2-yl) [Isomer 1] Refer to Chart WWW

Following procedures analogous to those described above, but using Isomer 1 of Preparation 153, the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR δ0.8–1.0, 1.3, 1.6–2.2, 2.5, 3.9, 6.8–7.2, 7.5, 7.9 ppm.

HRMS: 568.2271

R_f 0.27 (5% methanol in dichloromethane)

PREPARATION 154

Hexahydro-2H-1-benzopyran-2,4(3H)-dione (Formula DDDD-2, wherein n is 1) Refer to Chart DDDD

A solution of 0.42 g of platinum oxide and 1.66 g of the compound of formula DDDD-1 wherein n is 1 in 100 mL of acetic acid is placed on a Parr hydrogenation apparatus under an initial pressure of 50 psi of hydrogen for 1.5 h. The reaction mixture is then filtered through Celite and concentrated in vacuo to give a beige solid. The crude material is purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 0–5% methanol in chloroform to give 0.94 g of the title product as a white solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ4.84–4.80, 3.54, 3.40, 2.60–2.53, 2.08–2.02, 1.79–1.65, 1.62–1.54, 1.44–1.40 ppm.

^{13}C NMR ($CDCl_3$) δ203.0, 167.4, 74.3, 47.7, 45.6, 29.1, 23.5, 23.2, 19.7 ppm.

IR (mineral oil) 3092, 2768, 2714, 2695, 2662, 1657, 1614, 1577, 1444, 1352, 1345, 1340, 1323, 1308, 1295, 1287, 1260, 1244, 1211, 1188, 1057, 1004, 938, 909, 890, 843, 832, 600 cm^{-1}.

EI-MS: [M+]=168.

Anal. found: C, 64.16; H, 7.16.

PREPARATION 155

4a,5,6,7,8,8a-Hexahydro-4-hydroxy-3-[1-(3-nitrophenyl) propyl]-2H-1-benzopyran-2-one (Formula DDDD-4, wherein n is 1 and R_1 is ethyl) Refer to Chart DDDD

A solution of 3.17 g of aluminum trichloride in 30 mL of tetrahydrofuran is added to a solution of 2.00 g of the title compound of Preparation 154 and 1.82 g of 3-nitrobenzaldehyde in 20 mL of tetrahydrofuran. The resulting mixture is then stirred at room temperature for 2.5 h, at which time, 7.28 g of sodium carbonate decahydrate is added, and the reaction mixture is stirred an additional 20 min. The mixture is then dried over magnesium sulfate, filtered through Celite, and concentrated in vacuo to yield 6.05 g of a yellow gum. This crude material is immediately dissolved in 50 mL of tetrahydrofuran containing 0.73 g of cuprous bromide-dimethyl sulfide complex, and 13.1 mL of a 1.0M solution of triethyl aluminum in hexanes are added to the reaction mixture. After stirring at room temperature for 1 h, the reaction is quenched by the addition of water, and the resulting mixture is partitioned between ether and water. The organic layer is separated, washed with brine, and concentrated in vacuo to produce 4.0 g of a yellow oil. The crude material is purified by flash column chromatography eluting with 10–50% ethyl acetate in hexanes to yield 0.63 g of the title product as a yellow foam.

Physical characteristics are as follows:

MP 86°–91° C.

IR (mineral oil) 3085, 1635, 1569, 1528, 1448, 1394, 1365, 1349, 1325, 1307, 1288, 1270, 1251, 1244 cm^{-1}.

EXAMPLE 370

5-Cyano-N-[3-1-(4a,5,6,7,8,8a-hexahydro-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide (Formula DDDD-7, wherein n is 1, R_1 is ethyl, and R_2 is 5-cyano-2-pyridyl) Refer to Chart DDDD

A solution of 0.63 g of the title compound of Preparation 155 in 50 mL of ethanol with 0.3 g of 10% palladium on carbon is placed on a Parr hydrogenation apparatus at an initial pressure of 50 psi of hydrogen for 3 h. The reaction mixture is then filtered through Celite and concentrated in vacuo to give 0.519 g of crude intermediate. 0.25 g of this intermediate is immediately dissolved in 5 mL of methylene chloride, and 0.168 g of 5-cyano-2-pyridylsulfonyl chloride and 0.134 mL of pyridine are added to the solution. The resulting mixture is stirred at room temperature for 18 h. The reaction mixture is then purified by flash column chromatography on silica gel 60 (230–400 mesh) eluting with 0–2.5% methanol in chloroform to give 0.164 g of the title product as a white foam.

Physical characteristics are as follows:

MP 122°–125° C.

HRMS found: 468.1611

EXAMPLE 371

4-Cyano-N-[3-1-(4a,5,6,7,8,8a-hexahydro-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)propyl]phenyl]-benzenesulfonamide (Formula DDDD-7, wherein n is 1, R_1 is ethyl, and R_2 is 4-cyanophenyl) Refer to Chart DDDD

Following the general procedure of Example 370, and making non-critical variations, but substituting 4-cyanophenylsulfonyl chloride for 5-cyano-2-pyridylsulfonyl chloride, 0.236 g of the title compound is obtained as white foam.

Physical characteristics are as follows:

MP 127°–130° C.

HRMS found: 466.1583.

PREPARATION 156

4-Hexahydro-cyclohepta[b]pyran-2,4(3H,4aH)-dione (Formula DDDD-2, wherein n is 2) Refer to Chart DDDD

Following the general procedure of Preparation 154, and making non-critical variations, but substituting the cyclo-

heptylpyranone of Formula DDDD-1 wherein n is 2 for the cyclohexylpyranone of Formula DDDD-1 wherein n is 1, 0.337 g of the title compound is obtained as white solid.

Physical characteristics are as follows:

^{1}H NMR $CDCl_3$) δ4.97–4.91, 3.52, 3.42, 2.64–2.58, 2.22–2.11, 2.01–1.72, 1.59–1.36 ppm.

^{13}C NMR ($CDCl_3$) δ203.0, 167.2, 78.0, 52.1, 46.5, 32.1, 28.6, 27.1, 25.7, 21.3 ppm.

IR (mineral oil) 3074, 2791, 2755, 2736, 2687, 2637, 2608, 2585, 1655, 1625, 1586, 1500, 1480, 1443, 1333, 1324, 1293 (s), 1265, 1254, 1240, 1222, 1196, 1173, 1082, 1053, 1016, 909, 889, 832, 611 cm^{-1}.

EI-MS: [M+]=182.

Anal. found: C, 66.16; H, 7.90.

PREPARATION 157

5,6,7,8,9,9a-Hexahydro-4-hydroxy-3-[1-(3-nitrophenyl)-propyl]-cyclohepta[b]pyran-2(4aH)-one (Formula DDDD-4, wherein n is 2 and R_1 is ethyl) Refer to Chart DDDD

Following the general procedure of Preparation 155, and making non-critical variations, but substituting the title compound of Preparation 156 for the title compound of Preparation 154, 2.5 g of the title compound is obtained as a yellow foam.

Physical characteristics are as follows:

MP 75°–78° C.

IR (mineral oil) 3071, 2667, 1638, 1528, 1395, 1350, 1305, 1276, 1250, 1143, 1130, 1120, 1100, 1066, 782, 764, 741, 697, 685 cm^{-1}.

HRMS found: 345.1590.

Anal. found: C, 58.74; H, 5.63; N, 3.48.

EXAMPLE 372

5-Cyano-N-{3-[1-(2,4a,5,6,7,8,9,9a-octahydro-4-hydroxy-2-oxocyclohepta[b]pyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide (Formula DDDD-7, wherein n is 2, R_1 is ethyl, and R_2 is 5-cyano-2-pyridyl) Refer to Chart DDDD

Following the general procedure of Example 370, and making non-critical variations, but substituting the title compound of Preparation 157 for the title compound of Preparation 155, 0.206 g of the title compound is obtained as a white foam.

Physical characteristics are as follows:

MP 163°–166° C.

IR (mineral oil) 3352, 3128, 3100, 3073, 3029, 1760, 1726, 1641, 1608, 1593, 1584, 1411, 1397, 1355, 1295, 1282, 1242, 1207, 1173, 1125, 1106, 1086, 1074, 1028, 974, 967, 721, 701, 645, 638 cm^{-1}.

HRMS found: 481.1693.

PREPARATION 158

Octahydro-2H-cycloocta[b]pyran-2,4(3H)-dione (Formula DDDD-2, wherein n is 3) Refer to Chart DDDD

Following the general procedure of Preparation 154, and making non-critical variations, but substituting the cyclooctylpyranone of Formula DDDD-1 wherein n=3 for the cycloheptylpyranone of Formula DDDD-1 wherein n=2, 1.72 g of the title compound is obtained as a white solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ4.84–4.78, 3.61, 3.40, 2.75–2.70, 2.14–1.97, 1.90–1.72, 1.68–1.44 ppm.

^{13}C NMR ($CDCl_3$) δ204.2, 167.2, 78.2, 49.5, 46.1, 28.5, 27.3, 26.2, 24.7, 23.9, 22.1 ppm.

IR (mineral oil) 2659, 2617, 1650, 1612, 1579, 1444, 1356, 1332, 1307, 1287, 1265, 1244, 1227, 1209, 1041, 1035, 1003, 962, 946, 860, 832, 824 cm^{-1}.

HRMS found: 196.1100.

Anal. found: C, 67.06; H, 8.23.

PREPARATION 159

3-[2,2-Dimethyl-1-(3-nitrophenyl)propyl]-4a,5,6,7,8,9,10,10a-octahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one (Formula DDDD-4, wherein n is 3 and R_1 is t-butyl) Refer to Chart DDDD

A solution of 1.36 g of aluminum trichloride in 30 mL of tetrahydrofuran is added to a solution of 1.0 g of the title compound of Preparation 158 and 0.77 g of 3-nitrobenzaldehyde in 20 mL of tetrahydrofuran. The resulting mixture is then stirred at room temperature for 2.3 h, at which time, 3.06 g of sodium carbonate decahydrate is added, and the reaction mixture is stirred an additional 15 min. The mixture is then dried over magnesium sulfate, filtered through Celite, and concentrated in vacuo to yield a yellow foam. This crude intermediate is immediately dissolved in 5 mL of tetrahydrofuran for use in the second step.

A dry flask is charged with 0.82 g of activated zinc, 3 mL of tetrahydrofuran, 0.035 mL of dibromoethane, and 0.21 mL of a 1M solution of trimethylsilyl chloride in tetrahydrofuran. After the addition of each reagent the mixture is sonicated for 15 m at 45° C. The mixture is diluted further by the addition of 2 mL tetrahydrofuran and 1.32 mL of t-butyl iodide is added dropwise. The resulting mixture is sonicated for 3 h at 45° C. A separate mixture of 0.85 g of copper(I) cyanide and 0.80 g of lithium chloride in 4 mL of tetrahydrofuran is stirred at room temperature for 1 h until almost homogeneous and cooled to −30° C. The organozinc solution is then added via cannula to the copper cyanide solution and the resulting mixture is allowed to warm to 0° C. and to stir for 15 min. The reaction mixture is then cooled to −78° C., and the solution of crude intermediate prepared above is added. After stirring for 20 min at −78° C. and 30 min at 0° C., the reaction is quenched with a saturated solution of aqueous ammonium chloride and diluted with an additional 60 mL of tetrahydrofuran. The organic layer is separated, washed with water, and concentrated in vacuo to give 2.17 g of an orange foam. The crude material is then purified by flash column chromatography eluting with 10–30% ethyl acetate in hexanes followed by recrystallization in methylene chloride/hexanes to yield 0.60 g of the title product as a yellow solid.

Physical characteristics are as follows:

MP 158°–161° C.

IR (mineral oil) 3077, 2646, 1632, 1599, 1529, 1477, 1450, 1396, 1357, 1349, 1334, 1317, 1283, 1273, 1252, 1232, 1217, 1205, 1181 cm^{-1}.

EXAMPLE 373

5-Cyano-N-[3-[2,2-dimethyl-1-(4a,5,6,7,8,9,10,10a-octahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide (Formula DDDD-7, wherein n is 2, R_1 is t-butyl, and R_2 is 5-cyano-2-pyridyl) Refer to Chart DDDD

Following the general procedure of Example 370, and making non-critical variations, but substituting the title compound of Preparation 159 for the title compound of Preparation 157, 0.034 g of the title compound is obtained as white crystals.

Physical characteristics are as follows:

MP 182°–185° C.

IR (mineral oil) 3246, 3121, 3098, 2615, 1655, 1633, 1607, 1585, 1575, 1491, 1411, 1395, 1354, 1335, 1322, 1311, 1298, 1281, 1275, 1262, 1255, 1233, 1206, 1178, 1121, 1109, 1028, 977, 702, 657, 646, 635, 605 cm^{-1}.

HRMS found: 524.2216.

Anal. found: C, 63.86; H, 6.41; N, 7.82.

PREPARATION 160

(3(3R),4S)-3-[2-[1-[3-[bis(phenylmethyl)amino]phenyl]-propyl]-5-hydroxy-1,3-dioxo-5-(2-phenylethyl)octyl]-4-phenyl-2-oxazolidinone (Formula W-10 wherein R_1 is 2-phenylethyl) Refer to Chart W

To 100 mL of methylene chloride is added 5.0 g of the title compound of Preparation 95 (W-8) and the resulting solution cooled to −78° C. under an atmosphere of nitrogen. To that solution is added 1.0 mL of $TiCl_4$ and 1.63 mL of diisopropylethylamine, and the resulting solution is stirred for 1 hour. Then, 3.30 g of 1-phenyl-3-hexanone is added, and the reaction temperature raised to 0° C. for 2.5 hours. The reaction is then quenched by the addition of a saturated ammonium chloride solution, and the mixture is extracted with methylene chloride. The organic extract is washed with saturated sodium bicarbonate solution and evaporated in vacuo to yield 9.7 g of a yellow oil. Column chromatography on 900 g silica (elution with 10% hexane-methylene chloride, 100% methylene chloride) affords 3.30 g of the title compound as a yellow foam.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.33–7.23, 7.14, 7.04, 6.61–6.50, 5.45, 5.22, 4.71, 4.60, 4.48, 4.26, 3.33, 3.15–3.03, 2.58, 2.47–2.31, 1.93, 1.40–1.28, 1.24–1.13, 1.11–0.96, 0.88–0.77, 0.62–0.57 ppm.

MP 121°–126° C.

^{13}C NMR ($CDCl_3$) δ167.2, 167.1, 153.7, 142.6, 141.0, 138.2, 138.1, 129.6, 129.5, 129.2, 128.9, 128.8, 128.6, 128.4, 128.3, 127.0, 125.8, 125.6, 125.6, 73.1, 70.0, 69.9, 63.9, 57.9, 54.8, 54.7, 51.5, 51.4, 48.3, 41.3, 41.0, 40.8, 40.5, 29.8, 29.6, 27.1, 26.9, 16.8, 16.6, 14.6, 11.7, 11.6 ppm.

IR (mineral oil) 3525, 3061, 3026, 1777, 1720, 1690, 1601, 1495, 1361, 1335, 1238, 1199, 1104, 735, 698 cm^{-1}.

EI-MS: [M+]=736.

Anal. found: C, 78.03; H, 7.11; N, 3.79.

PREPARATION 161

(3S)-3-[1-[3-Bis(phenylmethyl)amino]phenyl]propyl]-5,6-dihydro-4-hydroxy-6-(2-phenylethyl-6-propyl-pyran-2-one (Formula W-11 wherein R_1 is 2-phenylethyl) Refer to Chart W

To 5 mL of dry tetrahydrofuran is added 2.7 g of the title compound of Preparation 160 and the resulting solution is cooled to 0° C. under an atmosphere of nitrogen. To that solution is added 0.45 mL of a 1M solution of potassium t-butoxide in tetrahydrofuran. The reaction mixture is then warmed to 20° C. and stirred for 2 hours. The reaction is quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer is washed with water, dried and evaporated in vacuo to yield 0.28 g of a yellow oil. Column chromatography on 80 g of silica gel (elution with 10–30% acetone/hexane) affords 0.195 g of a yellow foam. Crystallization from ethyl acetate/hexane yields 0.146 g of the title compound.

Physical characteristics are as follows:

MP 128°–131° C.

^{1}H NMR ($CDCl_3$) δ7.35–7.12, 6.73–6.64, 5.84, 4.73–4.57, 4.12, 2.69–2.61, 2.38–2.20, 1.95–1.65, 1.41–1.32, 0.98–0.87 ppm.

^{13}C NMR ($CDCl_3$) δ204.1, 204.0, 171.7, 171.4, 169.6, 140.9, 140.8, 140.6, 140.5, 140.4, 139.9, 139.8, 138.3, 129.7, 129.6, 129.5, 128.9, 128.6, 128.5, 128.4, 128.2, 128.1, 127.1, 126.9, 126.8, 126.7, 126.5, 126.4, 126.3, 126.2, 126.0, 125.9, 116.8, 112.6, 112.5, 112.4, 112.3, 112.2, 112.1, 112.0, 82.0, 81.9, 81.8, 80.4, 80.3, 58.6, 58.5, 54.5, 51.4, 50.4, 50.1, 49.9, 47.8, 47.4, 47.0, 46.6, 43.0, 42.9, 42.2, 41.9, 40.2, 40.1, 40.0, 39.2, 29.8, 29.7, 29.6, 29.1, 29.0, 26.8, 26.7, 24.7, 24.6, 24.3, 16.9, 16.5, 14.0, 12.3 ppm.

IR (mineral oil) 3023, 1637, 1599, 1584, 1575, 1494, 1347, 1300, 1257, 1243, 1234, 920, 731, 704, 695 cm^{-1}.

EI-MS: [M+]=573.

Anal. found: C, 81.53; H, 7.82; N, 2.34.

$[a]_D$ ($CHCl_3$)=−83°

PREPARATION 162

(3S)-3-[1-(3-Aminophenyl)propyl]-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-pyran-2-one (Formula W-12 wherein R_1 is 2-phenylethyl) Refer to Chart W

0.63 g of the title compound of Preparation 161 is dissolved in 45 mL of ethyl acetate and 15 mL of methanol. To that solution is added 0.47 g of 10% Pd/C, and the resulting mixture is hydrogenated at 50 psi for 2.5 hours. The reaction is then filtered through celite and concentrated in vacuo to yield 0.466 g of an off-white foam. Column chromatography on 80 g of silica gel (elution with 20–50% ethyl acetate-hexane) affords 0.389 g of the title compound as an off-white solid.

Physical characteristics are as follows:

MP 155°–159° C.

^{1}H NMR (CD_3OD) δ7.26–7.20, 7.15–7.04, 6.95, 6.81, 6.74, 6.54–6.51, 3.98–3.91, 2.68–2.54, 2.25–2.17, 2.02–1.67, 1.43–1.28, 0.99–0.87 ppm.

^{13}C NMR (CD_3OD) δ171.2, 171.0, 148.5, 148.2, 143.9, 130.4, 130.2, 127.8, 120.8, 117.8, 115.3, 107.4, 82.7, 44.6, 44.4, 41.8, 41.7, 41.5, 38.4, 31.8, 26.8, 26.7, 18.8, 15.6, 14.3 ppm.

IR (mineral oil) 3085, 3061, 3026, 1617, 1605, 1495, 1314, 1258, 1168, 1119, 1065, 1030, 923, 776, 699 cm^{-1}.

EI-MS: [M+]=393.

Anal. found: C, 76.13; H, 8.16; N, 3.37.

$[a]_D$ (MeOH)=−41°

EXAMPLE 374

N-[3-[1-(S)-[5,6,-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula W-13 wherein R_1 is 2-phenylethyl) Refer to Chart W

To a solution of 0.200 g of the title compound of Preparation 162 in 5 mL of methylene chloride is added 0.12 mL of pyridine. The resulting mixture is cooled to 0° C. and 0.132 g of 5-trifluoromethylpyridine-2-sulfonyl chloride is added. The reaction mixture is then stirred at room temperature for 1.5 h, concentrated in vacuo, and partitioned between ethyl acetate and water. The organic layer is concentrated in vacuo to 0.39 g of pink oil. Column chromatography on 50 g silica gel (elution with 20–50% ethyl acetate/hexane) affords 0.252 g of title compound as a white foam.

MP 170°–173° C.

^{1}H NMR (CD_3OD) δ8.95–8.92, 8.23–8.16, 8.04–8.00, 7.25–6.90, 4.86, 3.98–3.90, 3.31, 3.30, 2.69–2.46, 2.18–2.09, 1.96–1.65, 1.41–1.28, 0.99–0.81 ppm.

^{13}C NMR (CD_3OD) δ167.3, 147.7, 147.5, 142.9, 142.8, 137.7, 137.0, 129.5, 129.2, 126.9, 126.2, 126.1, 124.1, 122.6, 122.5, 120.3, 120.2, 81.8, 81.7, 43.6, 43.2, 40.9, 40.5, 37.5, 30.9, 25.8, 25.6, 17.9, 14.7, 13.3, 13.2 ppm.

IR (mineral oil) 3087, 3027, 1642, 1606, 1595, 1327, 1260, 1173, 1142, 1110, 1074, 1016, 720, 700, 613 cm^{-1}.

FAB-MS: [M+H]=603.

Anal. found: C, 61.79; H, 5.86; N, 4.48; S, 5.16.

$[a]_D$ (MeOH)=−310.

PREPARATION 163

(3S,6R)-3-[1-[3-bis(phenylmethyl)amino]phenyl]propyl]-5,6-dihydro-4-hydroxy-6-(2-phenylethyl-6-propyl-pyran-2-one (Formula FFF-2) Refer to Chart FFF

The title compound of Preparation 161 is chromatographed on a 5.1×30 cm Cyclobond I 2000 column in an ice bath at 90 mg per injection using an automated chromatographic system and a mobile phase of acetonitrile containing 0.1% diethylamine and 0.05% glacial acetic acid (v/v). The eluant is monitored at 260 nm, the flow rate is 45 mL/min, and appropriate fractions from multiple injections are combined and concentrated in vacuo to give 0.300 g of a dark oil. The oil is partitioned between ethyl acetate, saturated aqueous sodium bicarbonate solution, and water. The organic layer is separated and concentrated in vacuo. Column chromatography on 50 g of silica gel (elution with 10–20% acetone/hexane) affords 0.22 g of the title compound of the compound as a colorless oil.

Physical characteristics are as follows:

The retention time of the title compound is 57 min.

PREPARATION 164

(3S,6S)-3-[1-[3-bis(phenylmethyl)amino]phenyl]propyl]-5,6-dihydro-4-hydroxy-6-(2-phenylethyl-6-propyl-pyran-2-one (Formula FFF-3) Refer to Chart FFF

The title compound of Preparation 161 is separated as described in Preparation 163 above. Further purification as described in Preparation 163 affords 0.117 g of the title compound as a colorless oil.

Physical characteristics are as follows:

The retention time of the title compound is 66 min.

PREPARATION 165

(3S,6R)-3-[1-(3-aminophenyl)propyl]-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-pyran-2-one (Formula FFF-4) Refer to Chart FFF

Following the general procedure of Preparation 162, and making non-critical variations, but substituting the title product of Preparation 163 for the title product of Preparation 161, 0.022 g of the title compound is obtained.

Physical characteristics are as follows:

^{1}H NMR (CD_3OD) δ7.25–7.18, 7.15–7.12, 7.07–7.05, 6.97, 6.82-, 6.76–6.71, 6.53, 4.00–3.92, 2.67–2.54, 2.29–2.15, 2.06–1.92, 1.90–1.62, 1.46–1.28, 0.97–0.88 ppm.

EXAMPLE 375

(3S,6R)-N-[3-[1-[5,6,-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula FFF-5) Refer to Chart FFF

Following the general procedure of Example 374, and making non-critical variations, but substituting the title product of Preparation 165 for the title product of Preparation 162, 0.024 g of the title compound is obtained as a white foam.

Physical characteristics are as follows:

MP 156°–159° C.

^{1}H NMR (CD_3OD) δ8.90, 8.20–8.17, 8.02–7.99, 7.28–6.88, 4.00–3.90, 2.71–2.46, 2.20–2.10, 1.98–1.67, 1.41–1.28, 0.98–0.81 ppm.

EXAMPLE 376

(3S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran- 3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula W-13) Refer to Chart W

The title compound of Preparation 99 (formula W-12) 182 mg is dissolved in 5 mL of methylene chloride and 133 μL of pyridine added. The reaction is cooled to 0° C. and 142 mg of 5-trifluoromethyl-2-pyridinesulfonylchloride added. The reaction is stirred for 30 minutes and the methylene chloride is evaporated and the resulting material diluted with ethyl acetate. The organic solution is washed with water, brine and then dried over sodium sulfate. Evaporation of solvent gives 580 mg of crude product. Silica gel chromatography (50 g) eluting with 50% ethyl acetate/hexane affords 211 mg of the desired product as a white foam.

Physical characteristics are as follows:

Anal. found: C, 57.80; H, 5.95; N, 5.01; S, 5.64

$[\alpha]_D$ (18.094 mg/2 mL $CHCl_3$)=−30°

EXAMPLE 377

(3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula X-13) Refer to Chart X

The title compound of Preparation 107 (formula X-12) 170 mg is dissolved in 5 mL of methylene chloride and 136 μL of pyridine added. The reaction is cooled to 0° C. and 132 mg of 5-trifluoromethyl-2-pyridinesulfonylchloride is added. The reaction is stirred for 30 minutes and the methylene chloride is evaporated and the resulting material diluted with ethyl acetate. The organic solution is washed with water, brine and then dried over sodium sulfate. Evaporation of solvent gives crude product which is chromatographed over 50 g of silica gel eluting with 50% ethyl acetate/hexane affords 225 mg of the desired product as a white foam.

Physical characteristics are as follows:

$[\alpha]_D$ (mg/2 mL $CHCl_3$)=+29°

PREPARATION 166

(3S)(4R) 3-[2-[1-[3-[Bis(phenylmethyl)amino]phenyl]-propyl]-5-hydroxy-1,3-dioxo-5-phenethyloctyl]-4-phenyl-2-oxazolidinone (Formula X-10 where R_1 is phenethyl) Refer to Chart X

To 1.12 g of the title compound of Preparation 104 is added 20 mL of methylene chloride and the resulting solution cooled to −78° C. To that solution is added 237 μL of $TiCl_4$ followed by 400 μL of diisopropylethylamine and the resulting solution is stirred at −78° C. for 1 hour. To the aforementioned solution is added 776 μL of 1-phenyl-3-hexanone and stirring continued at −40° C. for 40 minutes and then the temperature is raised to −10° C. for 1.5 hours. The reaction is quenched with the addition of a saturated ammonium chloride solution, then extraction with methylene chloride and evaporation of the organic extracts. The crude material is chromatographed over 200 g of silica gel eluting with 10% hexane/methylene chloride to afford 870 mg of the title compound.

Physical characteristics are as follows:

IR (mineral oil) 2956, 2926, 2854, 1777, 1600, 1494, 1452, 698 cm^{-1}.

$[\alpha]_D$ (16.578 mg in $CHCl_3$)=+4°

Mass Spectrum: molecular ion at 736.

Anal. found. C, 78.00; H, 7.14; N, 3.61.

PREPARATION 167

(3R) 3-[1-[3-[Bis(phenylmethyl)amino]phenyl]propyl]-5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one (Formula X-11 where R_1 is phenethyl) Refer to Chart X

The compound of Preparation 166 (750 mg) is added to 5 mL of dry THF and potassium tert. butoxide (1.0M in THF; 1.2 mL) is added. The reaction is stirred at 20° C. for 30 minutes and then quenched by the addition of a saturated ammonium chloride solution. The reaction is extracted with ethyl acetate, the organic extracts washed with water and brine and finally evaporated to afford the crude product. Silica gel chromatography over 100 g of silica gel eluting with 15% ethyl acetate/hexane affords 511 mg of the title product.

Physical characteristics are as follows:

IR (mineral oil) 2956, 2855, 1628, 1599, 1577, 1494, 1385, 1364, 697 cm⁻1.

Anal. found: C, 81.30; H, 7.68; N, 2.30

Mass spectrum: molecular ion at 573.

$[\alpha]_D$ (18.116 mg/2 mL CH_3OH)=+38°

PREPARATION 168

(3R) 3-[1-[3-aminophenyl]propyl]-5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one (Formula X-12 where R_1 is phenethyl) Refer to Chart X

The compound of Preparation 167 (370 mg) is dissolved in 35 mL of ethyl acetate and 6 ml of methanol. To that solution is added 200 mg of 10% Pd on Carbon catalyst and the reaction is hydrogenated under 50 psi of hydrogen for 2 hours. The reaction is evaporated and chromatographed over 60 g of silica gel to yield 244 mg of the title compound.

Physical characteristics are as follows:

IR (mineral oil) 3025, 2954, 2871, 2854, 1635, 1619, 1604, 1494, 1456, 1383, 1378, 1256 cm⁻1.

$[\alpha]_D$ (16.764 mg/mL in CH_3OH)=+39°.

Mass spectrum: molecular ion at 393.

Anal. found: C, 75.79; H, 8.05; N, 3.27.

EXAMPLE 378

(3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula X-13 where R_1 is phenethyl) Refer to Chart X

The product of Preparation 168 (156 mg) is added to 5 mL of methylene chloride. To that solution is added 96 μL of pyridine and then the reaction is cooled to 0° C. To the aforementioned solution is added 102 mg of 5-trifluoromethyl-2-pyridinyl sulfonyl chloride. The reaction is stirred for 1 hour and then poured into ethyl acetate, washed with water, brine and dried with $MgSO_4$. The solvent is evaporated in vacuo and the resulting material chromatographed over 100 g of silica gel eluting with 50% ethyl acetate/hexane to yield 200 mg of the title compound.

Physical characteristics are as follows:

Mass spectrum: molecular ion at 602.

IR (mineral oil) 2953, 2922, 2870, 2853, 1642, 1605, 1459, 1457, 1326, 1259, 1180, 1171, 1141 cm⁻1.

UV (EtOH) λ_{max} (ε) 216 (22300), 264 sh (10700), 270 (11500), 279 (12100)

Anal. found: C, 57.53; H, 5.98; N, 4.84.

EXAMPLE 379

(3R,6S)-N-[3-[1-(5 6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula X-13 where R_1 is phenethyl) Refer to Chart X

The product of Example 378 is added to isopropanol and injected onto a 0.46×25 cm Cyclobond I 2000 column (Advanced Separations Technoloyies, Inc., Whippany, N.J.). The column is in an ice-water bath. The sample is eluted at 1.0 mL/min. with acetonitrile containing 0.1% diethylamine and 0.6% glacial acetic acid (V/V). The monitor is set at 250 nm. The earlier eluting diastereomer is identical to the compound of Example 298. The second eluting diastereomer is purified over 60 g of silica gel eluting with 40% ethyl acetate/hexane to afford 13 mg of the title compound.

Physical characteristics are as follows:

Opposite stereochemistry at C-6 to the compound of Example 298.

^{1}H-NMR (CD_3OD, δ) 8.91, 8.19, 8.16, 8.02, 7.99, 7.25, 7.18, 7.15, 7.13, 7.11, 7.04, 6.97, 6.89, 6.75, 3.95,2.69, 2.64, 2.53, 2.48, 2.13, 1.91, 1.71, 1.68, 1.37, 1.19, 1.17, 1.14, 0.94, 0.92, 0.89, 0.85, 0.83, 0.80, 0.93.

PREPARATION 169

(3S)-3-[(3-Bis(phenylmethyl)amino)phenyl]-4,4-dimethylpentanoic acid methyl ester (Formula LLL-9) Refer to Chart LLL

To anhydrous methanol (2 mL) at room temperature is added titanium (IV) chloride (0.07 mL). The resulting light green solution is stirred for 2 h, treated with the compound of formula LLL-2 wherein R is phenyl (100 mg), prepared by procedures analogous to those described in Chart FF, and refluxed for 18 h. The reaction mixture is allowed to cool and is partitioned between 1N HCl and diethyl ether. The organic layer is separated washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification by flash chromatography eluting with hexane/ethyl acetate (95:5) affords the title compound (58 mg) as a light amber oil.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.32–7.20, 7.04, 6.61–6.48, 4.61, 3.48, 2.85–2.80, 2.72–2.55, 0.75 ppm

^{13}C NMR ($CDCl_3$) δ173.69, 148.45, 142.51, 138.91, 128.53, 128.17, 126.78, 117.98, 114.49, 110.89, 54.54, 52.24, 51.40, 35.56, 33.65, 27.87 ppm

MS (EI) m/z 415.

PREPARATION 170

(3S)-3-[(3-Bis(phenylmethyl)amino)phenyl]-4,4-dimethylpentanoic acid (Formula LLL-10) Refer to Chart LLL

The compound of formula LLL-9 (406 mg) of Preparation 169 is slurried in glacial acetic acid (2.6 mL) and 6N sulfuric acid. The reaction mixture is refluxed for 5 h, allowed to cool and is partitioned between water and diethyl ether. The aqueous layer is separated and extracted two more times with diethyl ether. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resulting light brown residue is dissolved in diethyl ether and treated with dicyclohexylamine (0.16 mL) at 0° C. The solids are isolated, washed with diethyl ether and dried in vacuo. The light brown solid is suspended in diethyl ether and washed with 0.25N HCl. The organic layer is washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo, affording the title product (54 mg) as a light brown amorphous solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.31–7.19, 7.04, 6.61–6.48, 4.61, 2.81–2.56, 0.74 ppm

^{13}C NMR ($CDCl_3$) δ179.15, 148.56, 142.28, 138.83, 128.55, 128.23, 126.76, 117.90, 114.49, 110.98, 54.51, 51.83, 35.45, 33.67, 27.84 ppm

MS (EI) m/z 401.

PREPARATION 171

N-[(S)-4-Benzyl-2-oxazolidinone]3-aminocinnamate amide (Formula HHH-4) Refer to Chart HHH

A 1 liter round-bottomed flask with nitrogen inlet and addition funnel is charged with 10.02 g of commercially available (S)-4-benzyl-2-oxazolidinone and 260 mL of tetrahydrofuran and then cooled to −78° C. To the aforementioned solution is added 37 mL of n-butyl lithium during which time a white solid separates from the reaction solution. To that suspension is added 11.46 g of trans-3-nitrocinnamic acid chloride (prepared from the treatment of commercially available 3-nitrocinnamic acid with oxalyl chloride) in a small volume of THF. The resulting pale yellow homogeneous solution is allowed to warm to room temperature and quenched with a saturated ammonium chloride solution and is extracted with ethyl acetate. The organic layer is separated, washed with brine and water,

dried over magnesium sulfate, filtered and concentrated to give a reddish brown syrup (formula HHH-3 in Chart HHH) which is used without further purification. The aforementioned crude reaction mixture is added to ethanol containing 64.18 grams of $SnCl_2.2H_2O$ and that mixture heated at reflux for 20 minutes. The reaction is cooled to room temperature and poured into ice. The mixture is brought to pH 9–10 with saturated aqueous Na_2CO_3. The mixture is filtered and the filter cake washed extensively with ethyl acetate. The filtrate is washed with brine and the organic phase is dried (Na_2SO_4), filtered, and concentrated in vacuo to give a yellow solid. Recrystallization from ethanol gives 11.56 g of the title product.

Physical characteristics are as follows:

IR (mineral oil) 3450, 3369, 2924, 1771, 1678, 1620, 1462, 1392, 1357, 1347, 1214 cm^{-1}

$[\alpha]_D$ (14.418 mg/mL in $CHCl_3$)=+51°

PREPARATION 172

N-[(S)-4-Benzyl-2-oxazolidinone]3-(bis(phenylmethyl) amino) cinnamate amide (Formula HHH-5) Refer to Chart HHH

The amine of formula HHH-4 from Preparation 172 (10.13 g), 10.48 g of potassium carbonate, 8.3 mL of benzyl bromide and 100 mL of acetonitrile is heated at reflux for 3 hours. The reaction is cooled to room temperature and partitioned between water and ethyl acetate. The aqueous is extracted several additional times with ethyl acetate. The combined ethyl acetate extracts are dried (Na_2SO_4), filtered and concentrated in vacuo. The residue is purified via silica gel chromatography eluting with 25% ethyl acetate/hexane to yield 8.87 g of the title product.

Physical characteristics are as follows:

^{13}C-NMR ($CDCl_3$, ppm) 165, 153, 149, 147, 138, 135, 129.6, 129.3 128.8, 128.6, 127, 126.9, 126.5, 116.54, 116.50, 114, 113, 65, 55, 54, 37

IR (mineral oil) 2954, 2870, 2854, 1776, 1677, 1616, 1595, 1493, 1454, 1353, 1209, 988 cm^{-1}

PREPARATION 173

(3S)(4S) 3-[3-(3-(bis(phenylmethyl)aminophenyl) pentanoyl]-4-phenyl-2-oxazolidinone (Formula HHH-6) Refer to Chart W

A 100-mL, three-necked flask equipped with a stir-bar, 25-mL pressure-equalizing addition funnel, and a nitrogen inlet is charged with copper(I) bromide dimethyl sulfide complex (1.69 g), 20 mL of tetrahydrofuran and 10 mL of dimethyl sulfide. The addition funnel is charged with the title compound of Preparation 172 (2.747 g) and 10 mL of tetrahydrofuran. The reaction mixture is cooled to −40° C. and ethyl magnesium bromide (5.5 mL of a 3.0M solution in ether) is added dropwise over 5 min. The resulting black mixture is stirred another 10 min at −40° C. and then allowed to warm to −10° C. The solution of the title compound of Preparation 172 in tetrahydrofuran is added dropwise to the reaction mixture over 17 min. The addition funnel is then rinsed with another 3 mL of tetrahydrofuran, and the reaction mixture is stirred for 2.5 h at ca. −40° to −60° C. The reaction is quenched by pouring the mixture into 50 mL of saturated aqueous ammonium chloride solution, and the organic solvents are removed by concentration in vacuo. The resulting residue is partitioned between 75 mL of ethyl acetate and 50 mL of water and filtered through glass wool. The organic layer is then separated, washed with two 100-mL portions of 10% ammonium hydroxide solution and 50 mL of brine, dried over magnesium sulfate, filtered and concentration in vacuo to yield 3.59 g of a yellow oil. Column chromatography on 150 g of silica gel (elution with 5–15% ethyl acetate/hexane) affords two diastereomeric products. 1.602 g of the title compound (the less polar diastereomer) is isolated as a pale yellow oil

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.32–7.17, 7.06, 6.60, 6.55, 4.63, 4.43–4.37, 4.00, 3.85, 3.37, 3.20, 3.08, 3.02–2.92, 2.62, 1.71–1.48, 0.73 ppm]

Also isolated from the column is 0.310 g of the more polar diastereomer as a pale yellow oil.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ7.32–7.18, 7.12, 7.05, 6.64–6.56, 4.63, 4.60–4.52, 4.08–4.04, 3.48–3.38, 3.07–2.96, 2.48, 1.69–1.48, 0.73 ppm.

In addition, fractions containing 0.708 g of a ca. 1:4 ratio mixture of the less polar to more polar diastereomers are collected from the column.

PREPARATION 174

(3S,6S)-3-[1-(3-aminophenyl)propyl]-5,6-dihydro-4-hydroxy-6-(2-phenylethyl)-6-propyl-2H-pyran-2-one (Formula FFF-6) Refer to Chart FFF

Following the general procedure of Preparation 162, and making non-critical variations, but substituting the title product of Preparation [U-141164] for the title product of Preparation 161, 0.040 g of crude title compound is obtained. This compound is used immediately in the next step without further purification.

EXAMPLE 380

(3S,6S)-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula FFF-7) Refer to Chart FFF

Following the general procedure of Example 374, and making non-critical variations, but substituting the title product of Preparation 174 for the title product of Preparation 162, 0.015 g of the title compound is obtained as a white foam.

Physical characteristics are as follows:

^{1}H NMR (CD_3OD) δ8.95, 8.25–8.21, 8.07–8.02, 7.25–6.93, 3.94–3.88, 2.70–2.51, 2.20–2.18, 1.97–1.66, 1.40–1.30, 0.92–0.81 ppm.

Thus, for example, the compounds of the present invention include the following individual stereoisomers:

5-cyano-N-[3-(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-cyano-N-[3-(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-cyano-N-[3-(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(S)-(3,3,2-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-cyano-N-[3-(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

N-[3-(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(R)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(S)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(S)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(R)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-amino-N-[3-(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-amino-N-[3-(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-amino-N-[3-(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-amino-N-[3-(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

N-[3-(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R)-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

N-[3-(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(S)-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

N-[3-(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R)-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

N-[3-(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(S)-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(R)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3-(R)-[-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3-(S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(R)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]1-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]1-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(R)-[1-[4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(S)-[1-[4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3-(R)-[1-[4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3-(S)-[1-[4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3-(R)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3-(S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6(R)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6(S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6(R)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6(S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3(R)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3(R)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3(S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

4-Trifluoromethyl-N-[3(S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6(R)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6(S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6(R)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6(S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6(R)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6(S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6(R)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6(S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(R)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(R)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

N-[3(R)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(R)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3(R)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(S)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3(S)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(R)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3(S)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(S)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-Amino-N-[3(R)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(R)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(R)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(R)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenylethyl)-6-propyl- 2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(R)-(1-[6(R)-(2-[4-fluorophenyl]ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(R)-(1-[6(S)-(2-[4-fluorophenyl]ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(S)-(1-[6(R)-(2-[4-fluorophenyl]ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(S)-(1-[6(S)-(2-[4-fluorophenyl]ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

N-[3(R)-(1-[5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3(S)-(1-[5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-Amino-N-[3(R)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(S)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(R)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(S)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

N-[3(R)-(1-[6,6-Bis(2-phenylethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3(S)-(1-[6,6-Bis(2-phenylethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3(R)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide,

N-[3(S)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-aminopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-aminopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)- 2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-aminopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-aminopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-aminopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-aminopyridine-2-sulfonamide,

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-aminopyridine-2-sulfonamide,

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-aminopyridine-2-sulfonamide,

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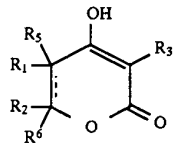

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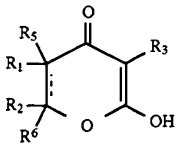

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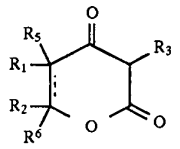

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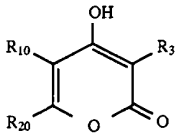

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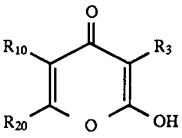

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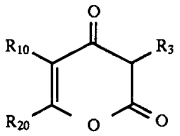

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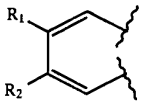

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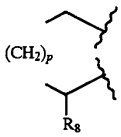

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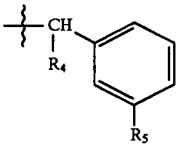

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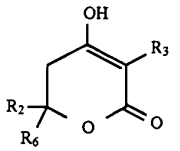

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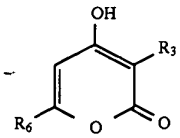

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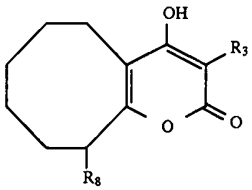

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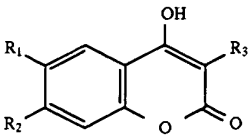

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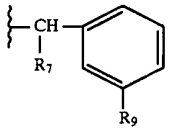

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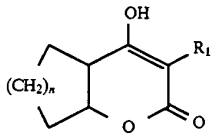

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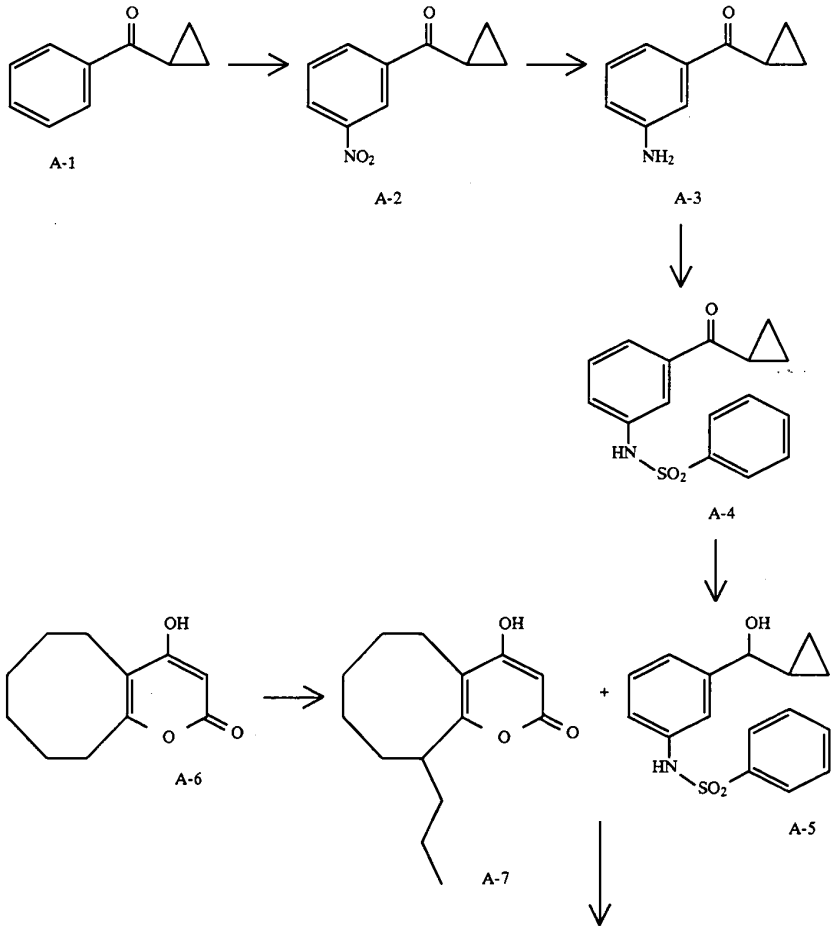

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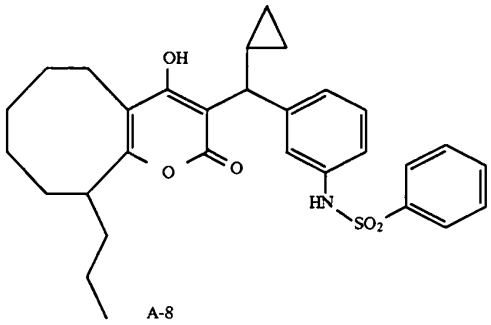

A-8

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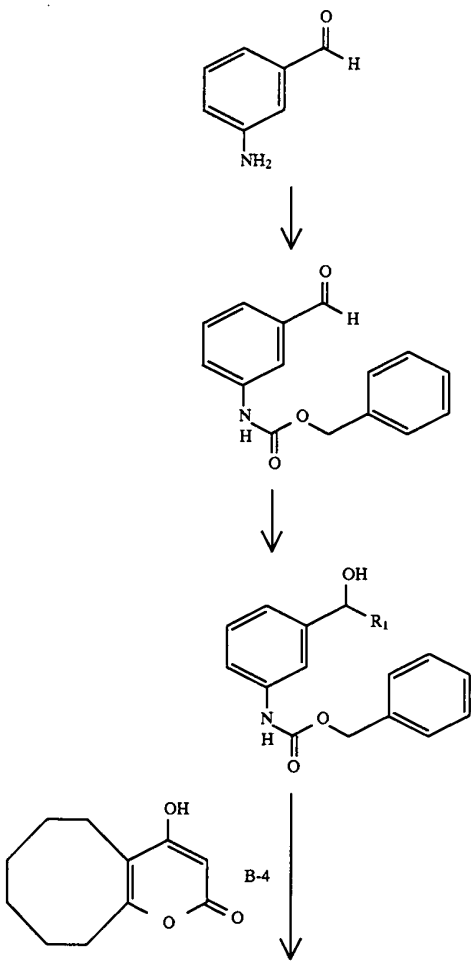

B-1

B-2

B-3

B-4

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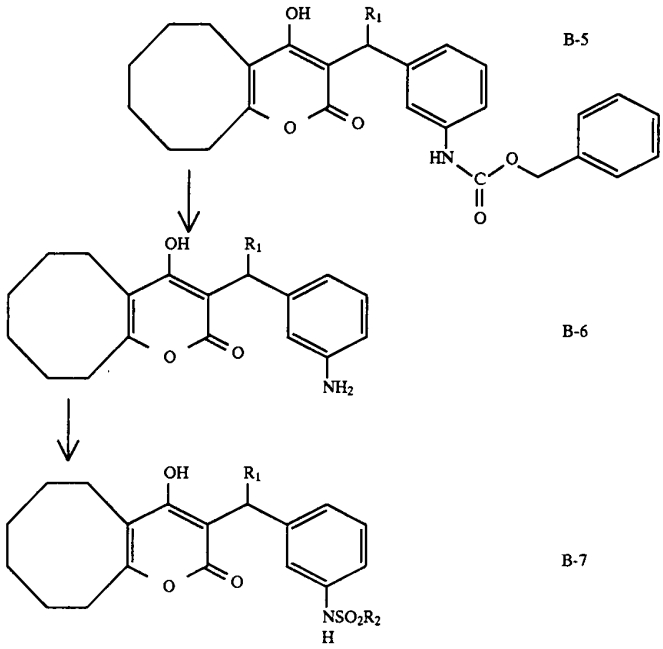
CHART B



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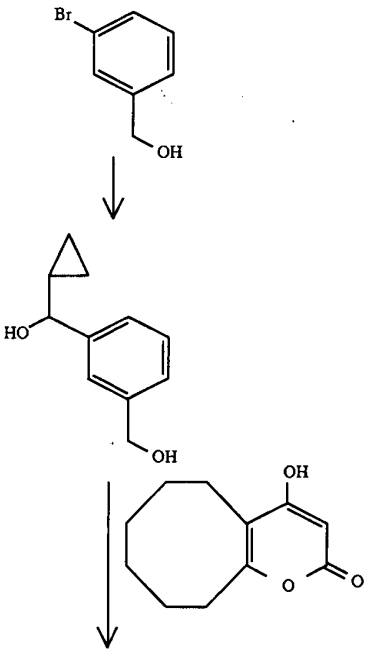

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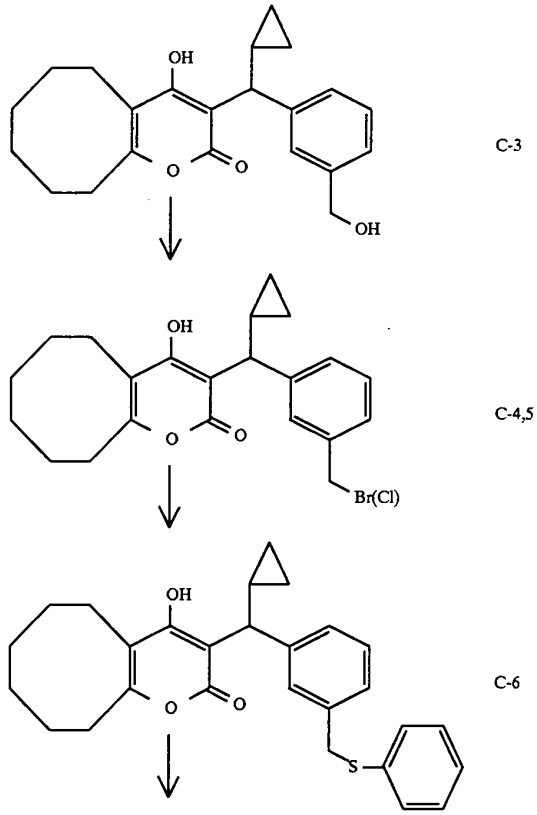

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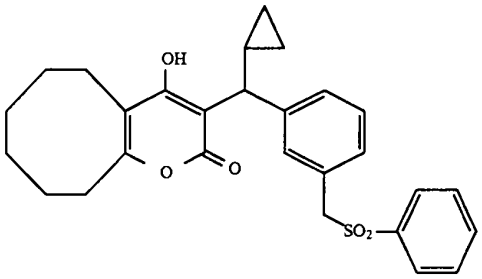

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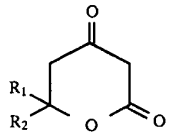

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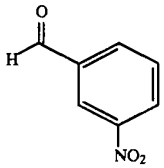

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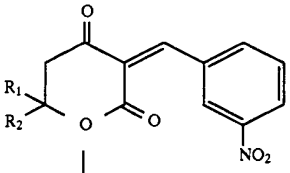

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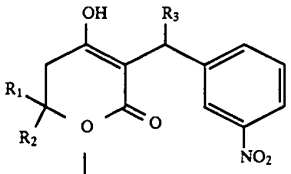

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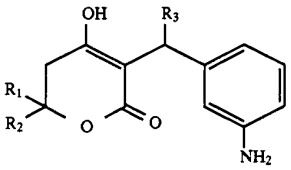

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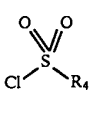

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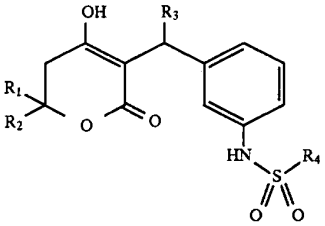

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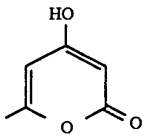

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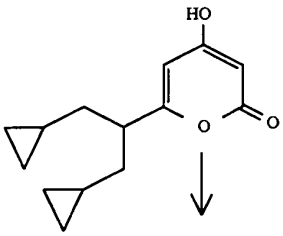

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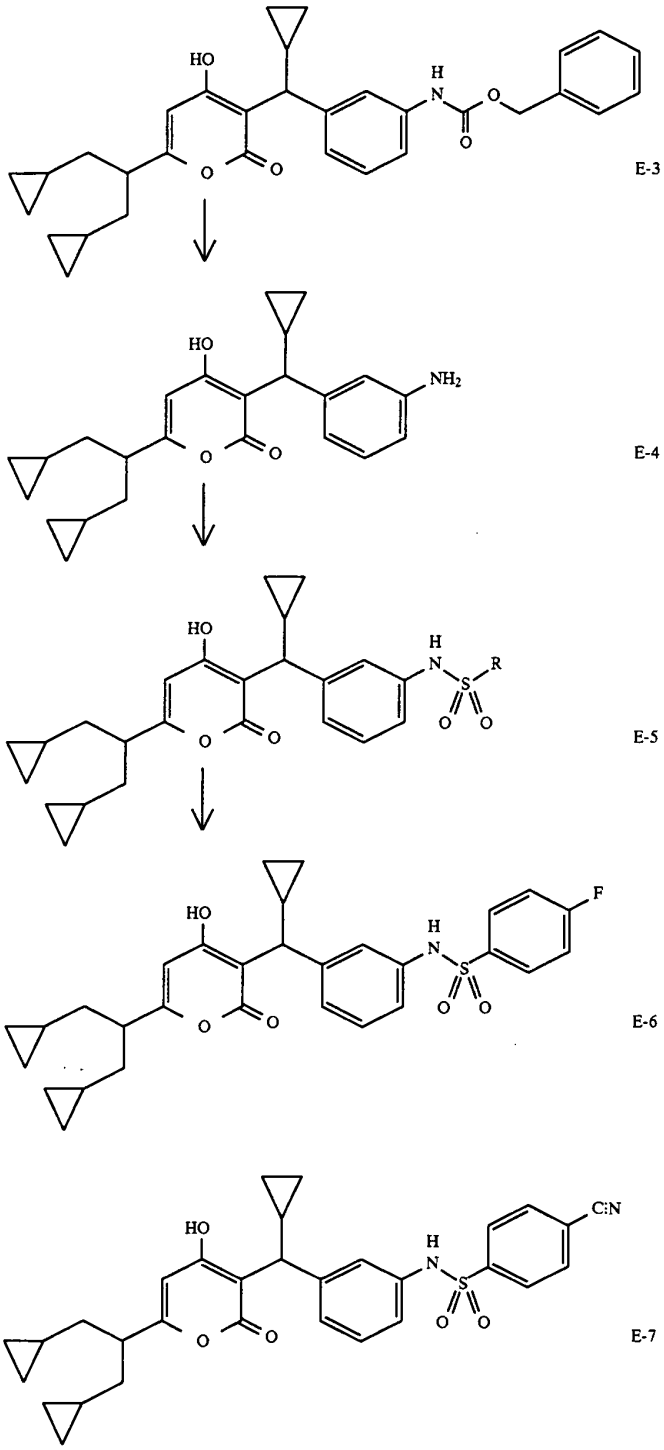

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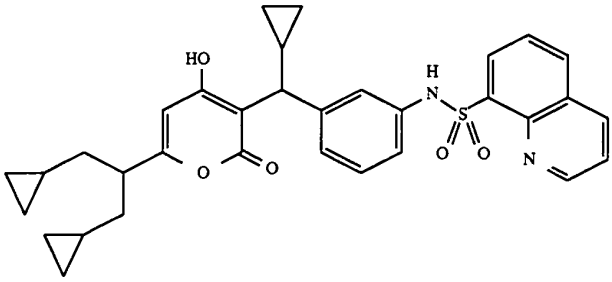

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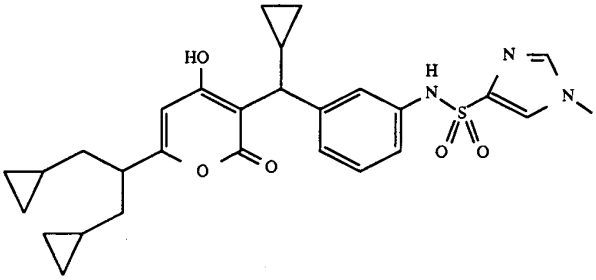

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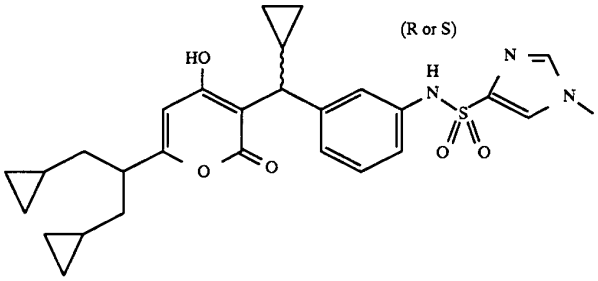

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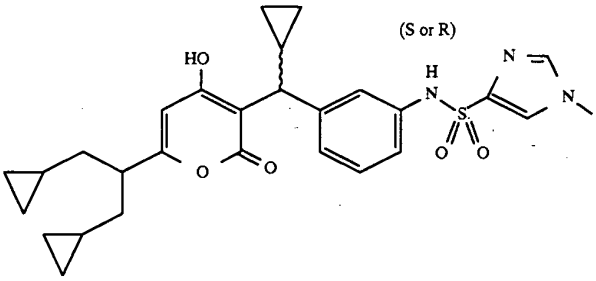

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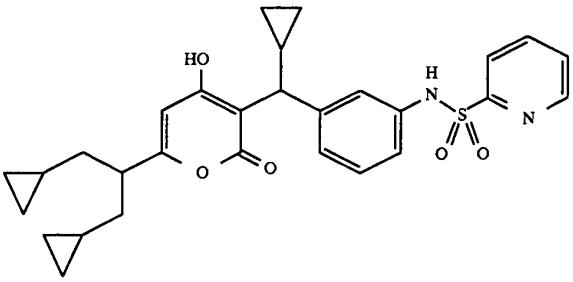

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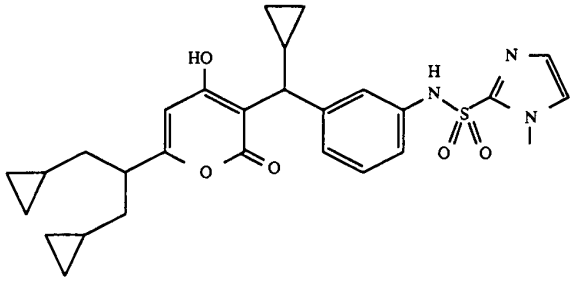

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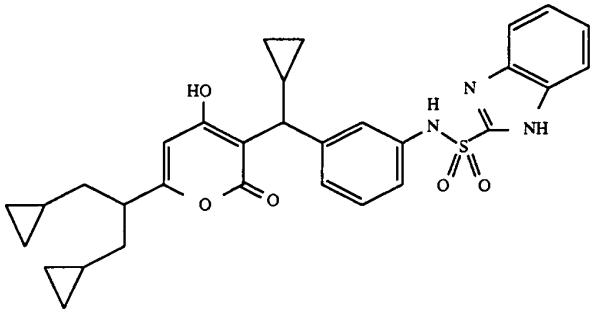

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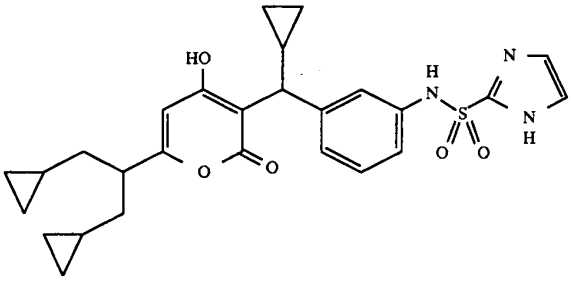

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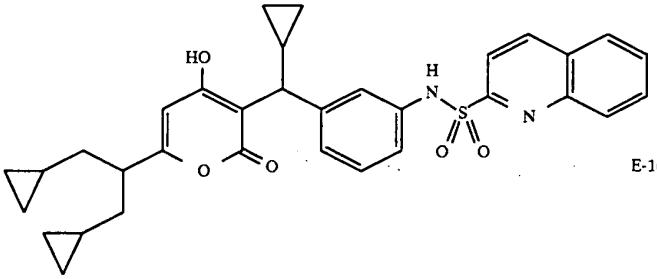

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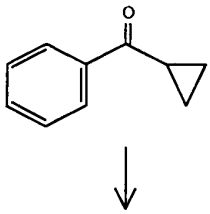

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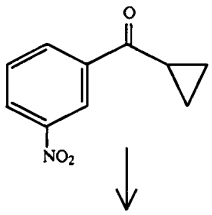
CHART F



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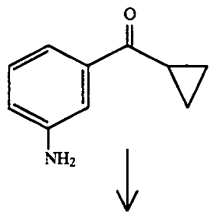

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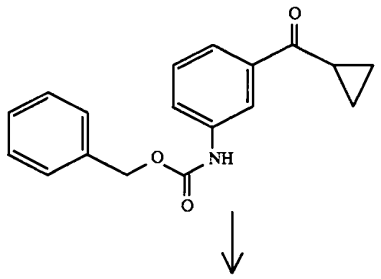

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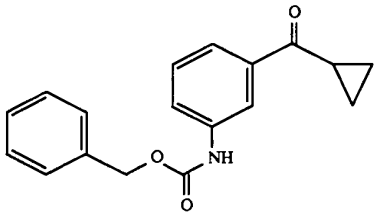

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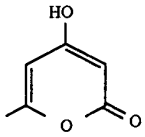

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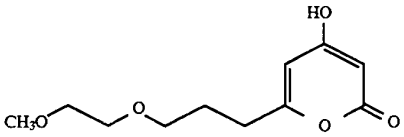

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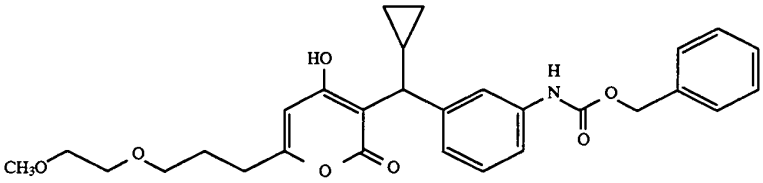

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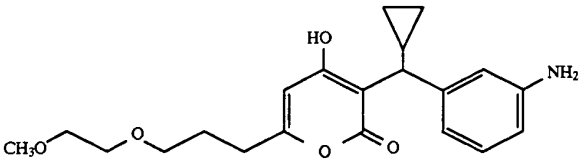

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CHART G

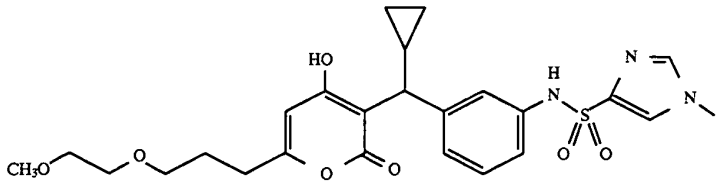

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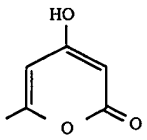
CHART H



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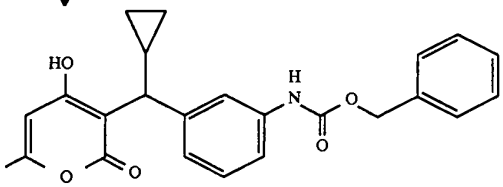

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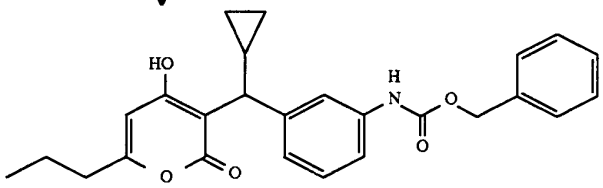

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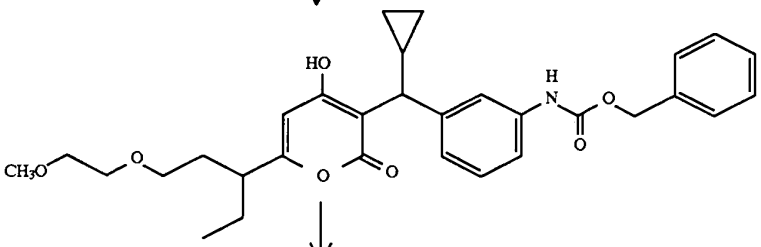

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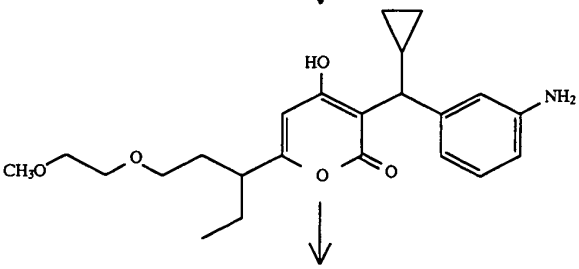

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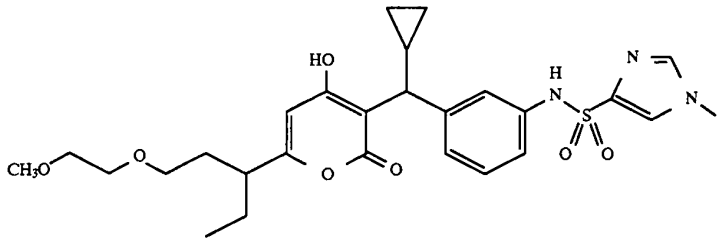
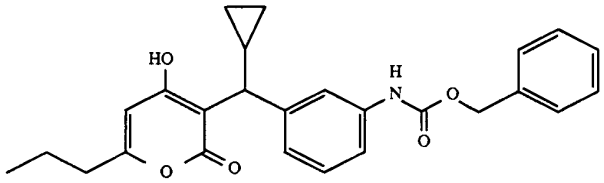
CHART H



H-5

CHART I



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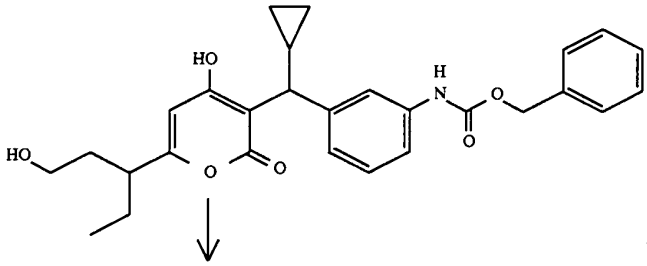

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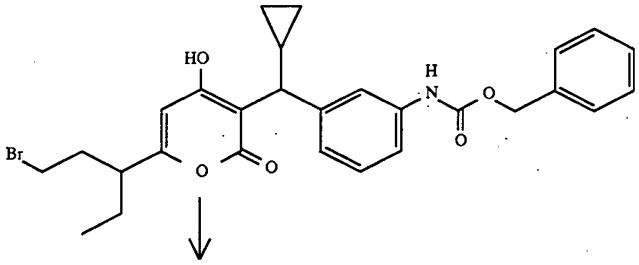

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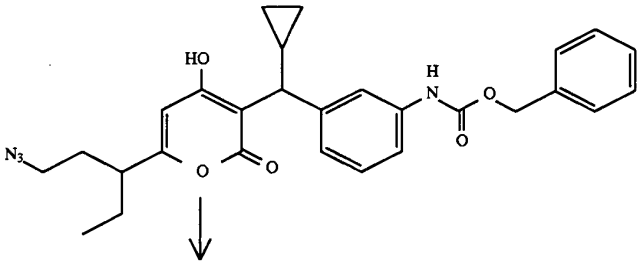

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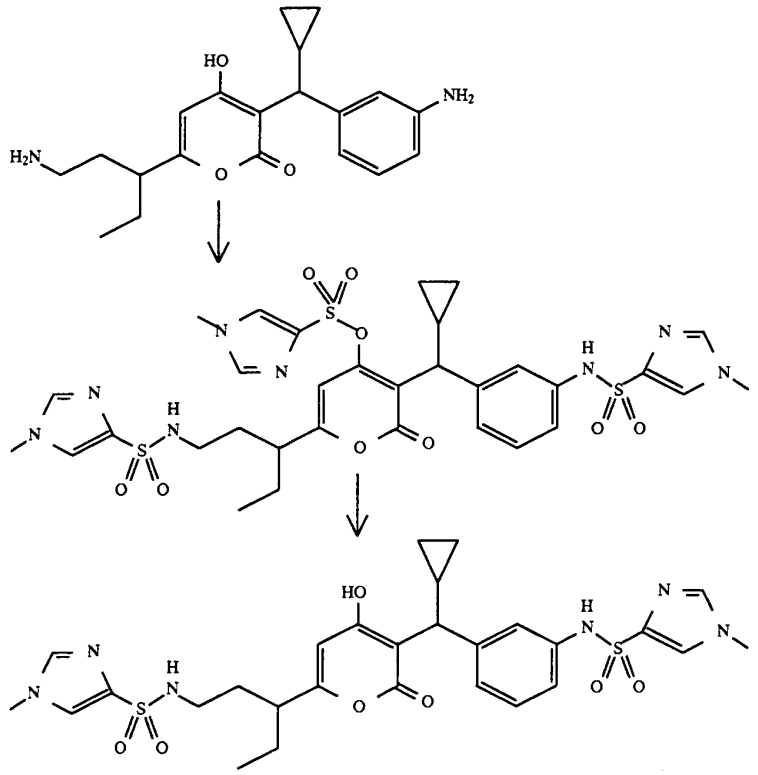
CHART I



I-4

I-5

I-6

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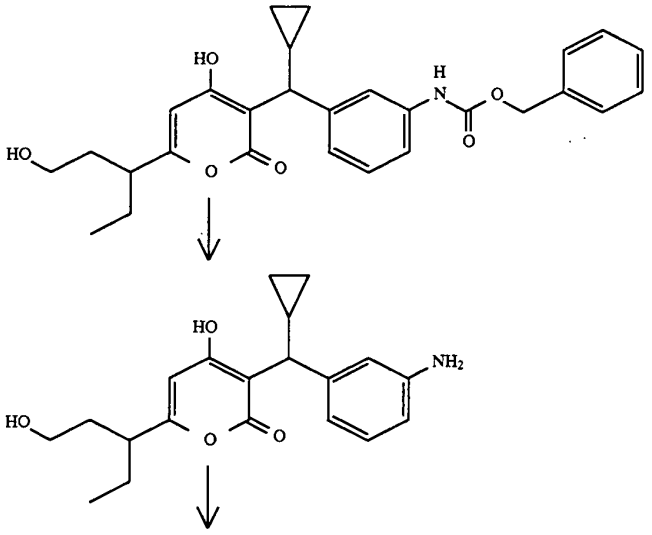

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J-1

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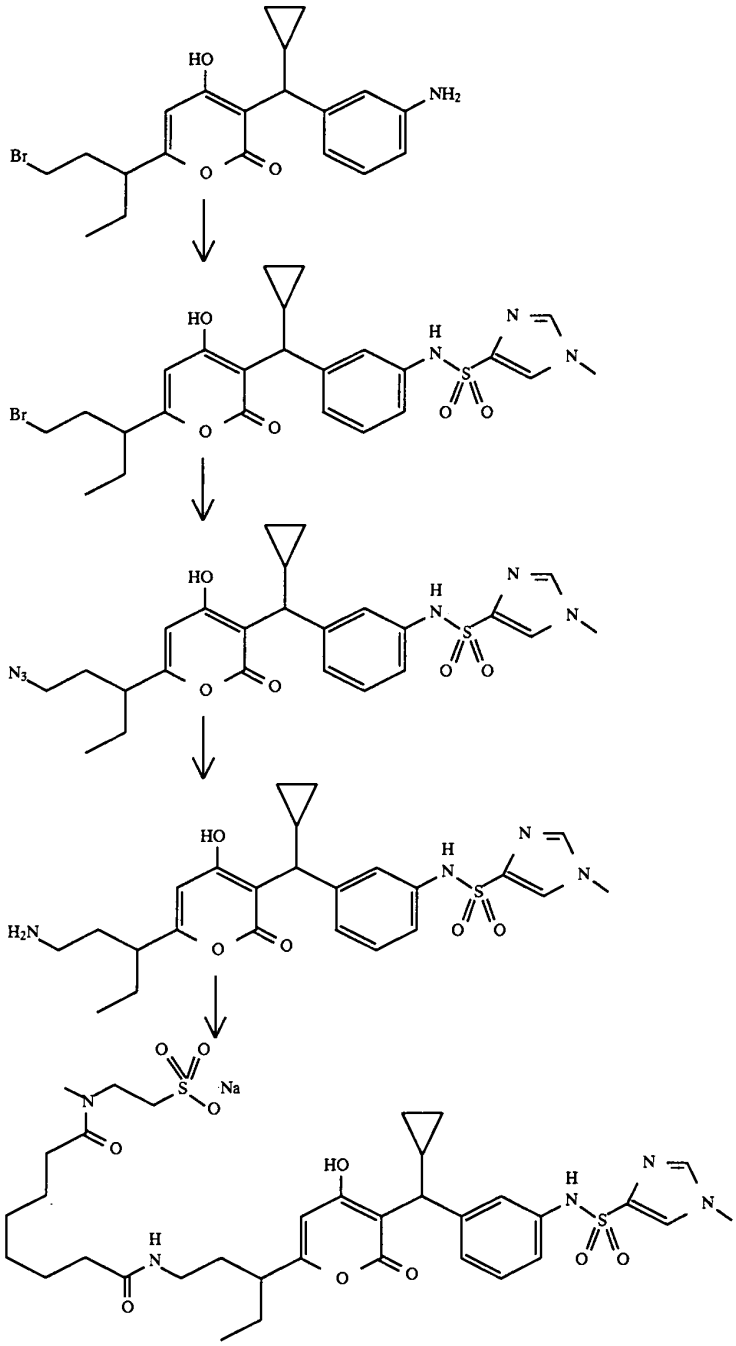

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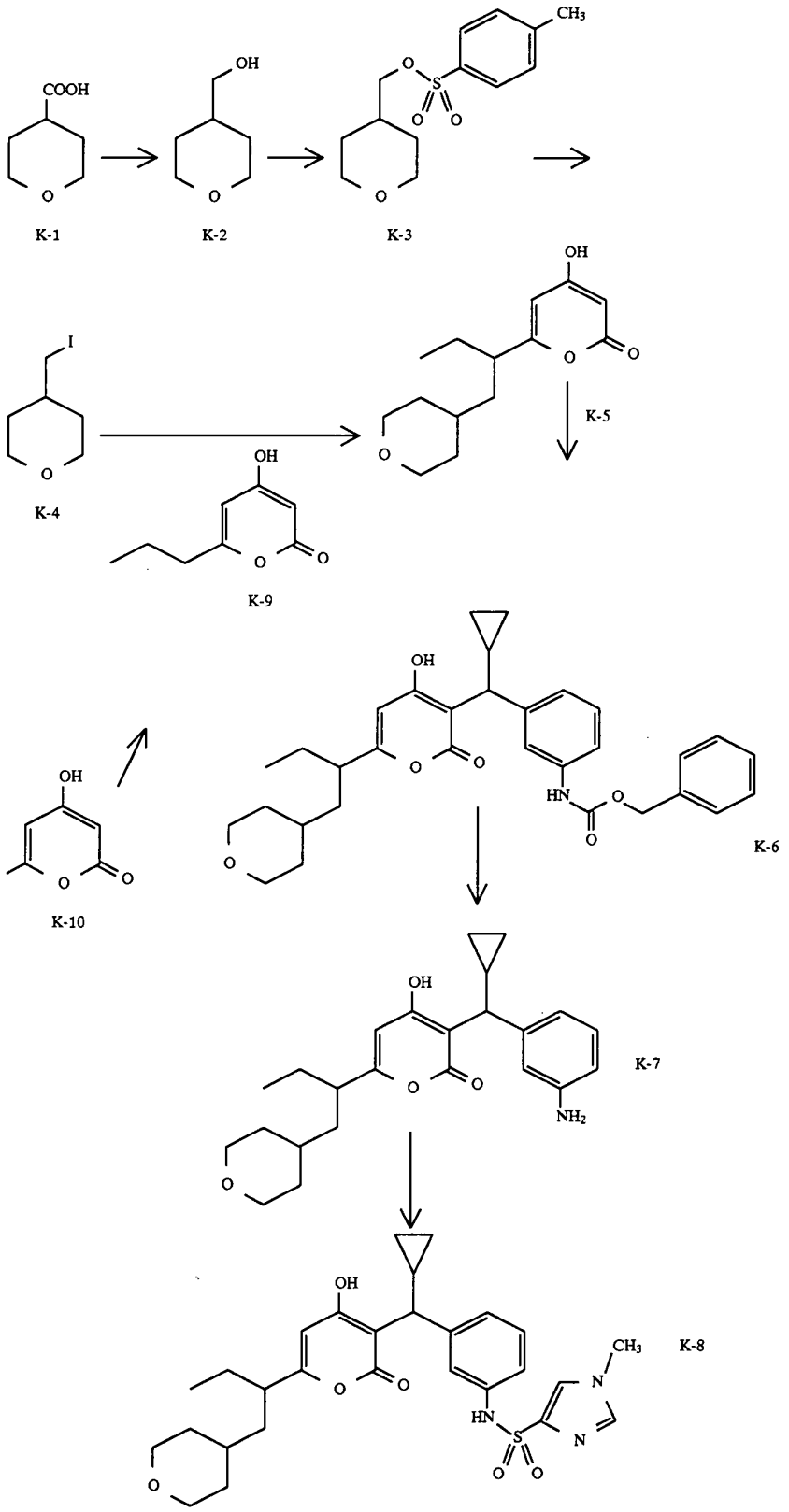

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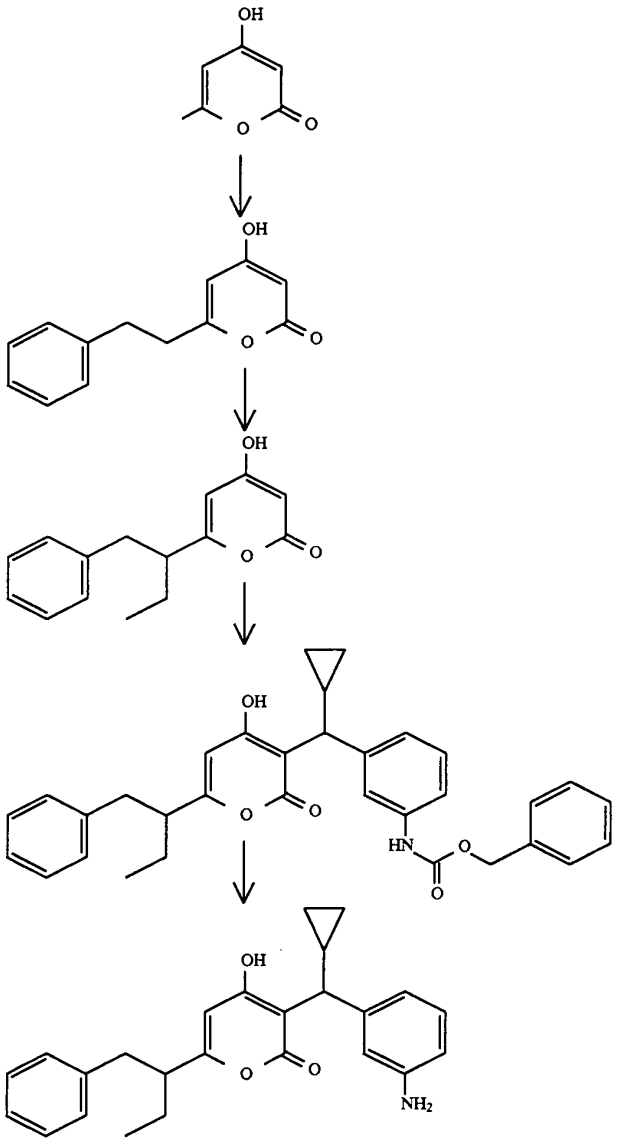

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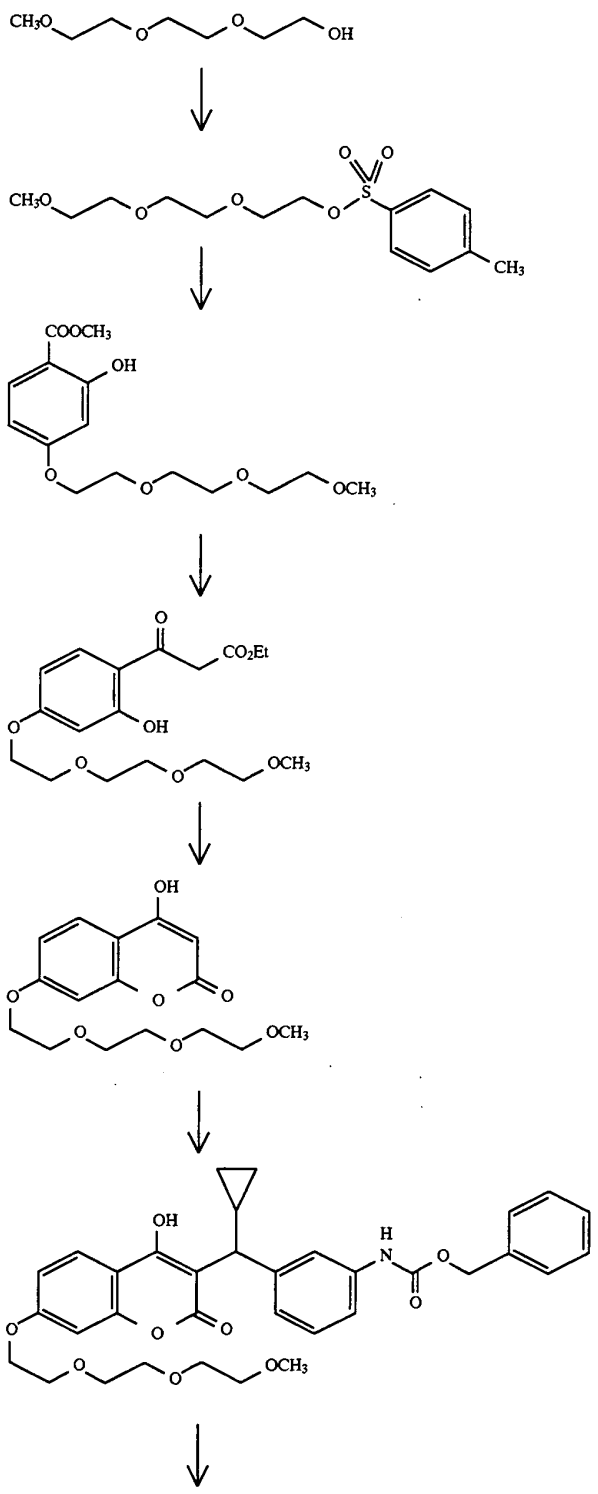

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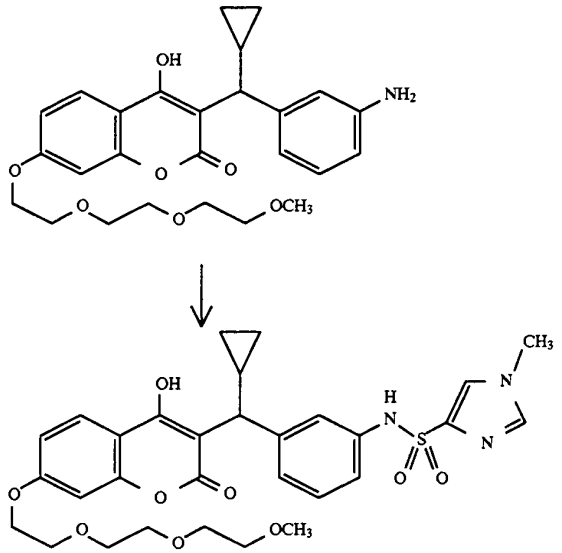

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M-8

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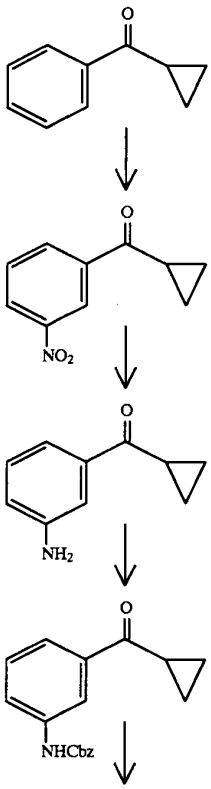

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N-2

N-3

N-4

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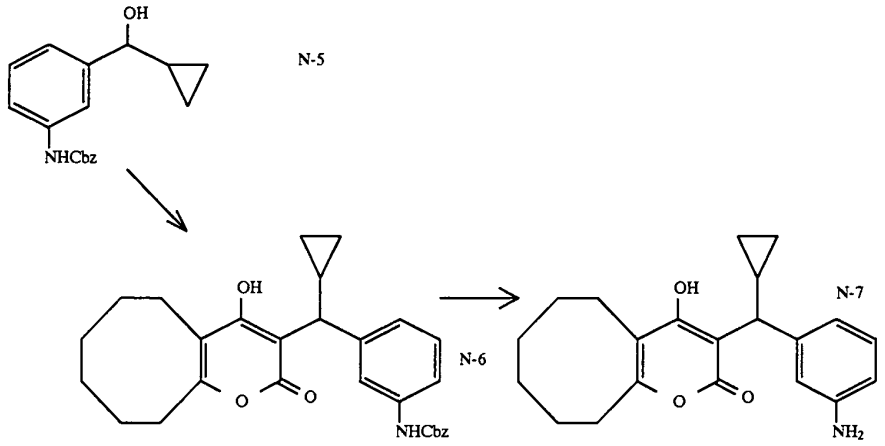
CHART N



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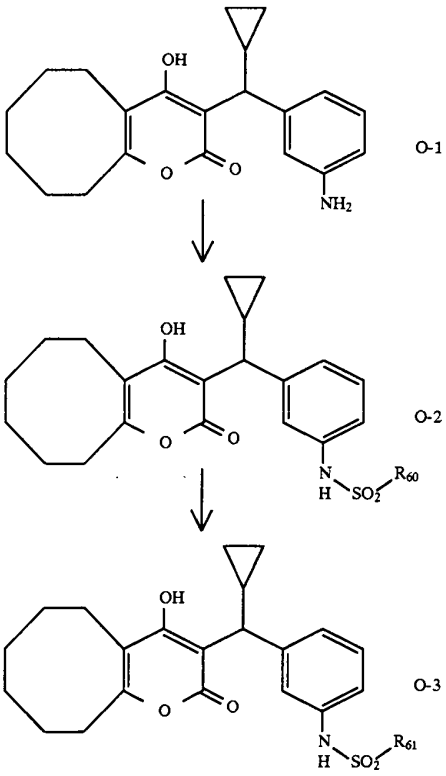

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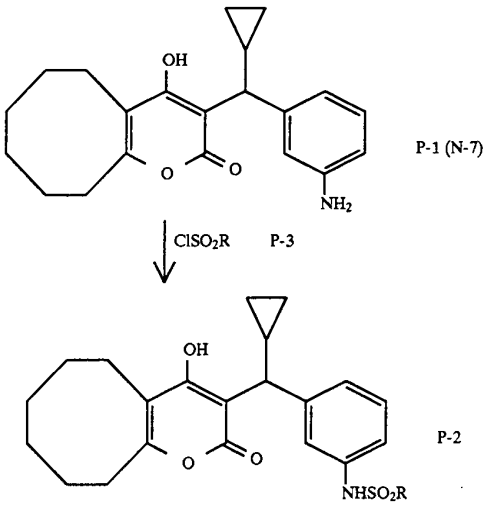

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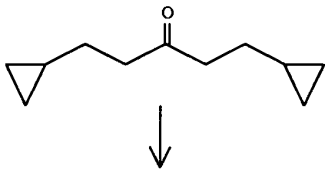

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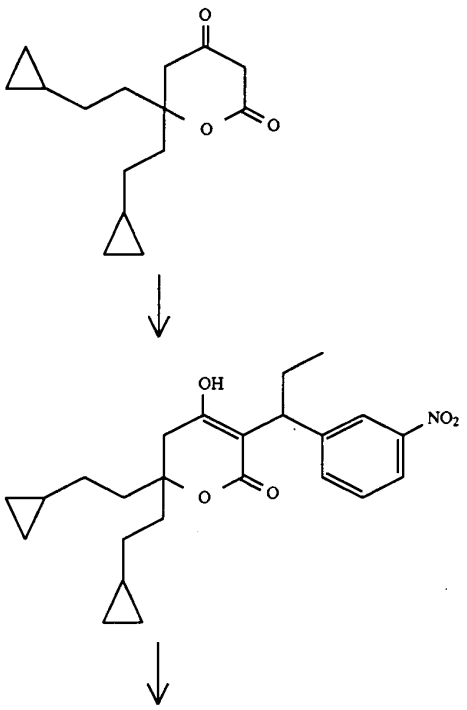

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Q-3

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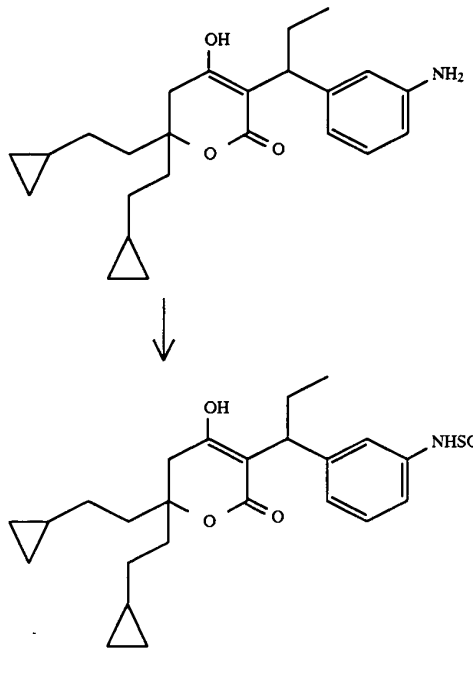
CHART Q



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Q-5

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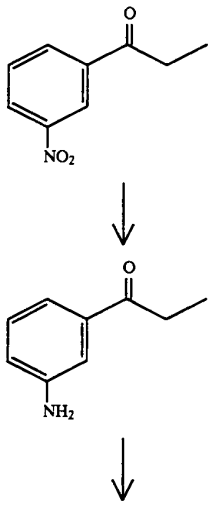

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R-2

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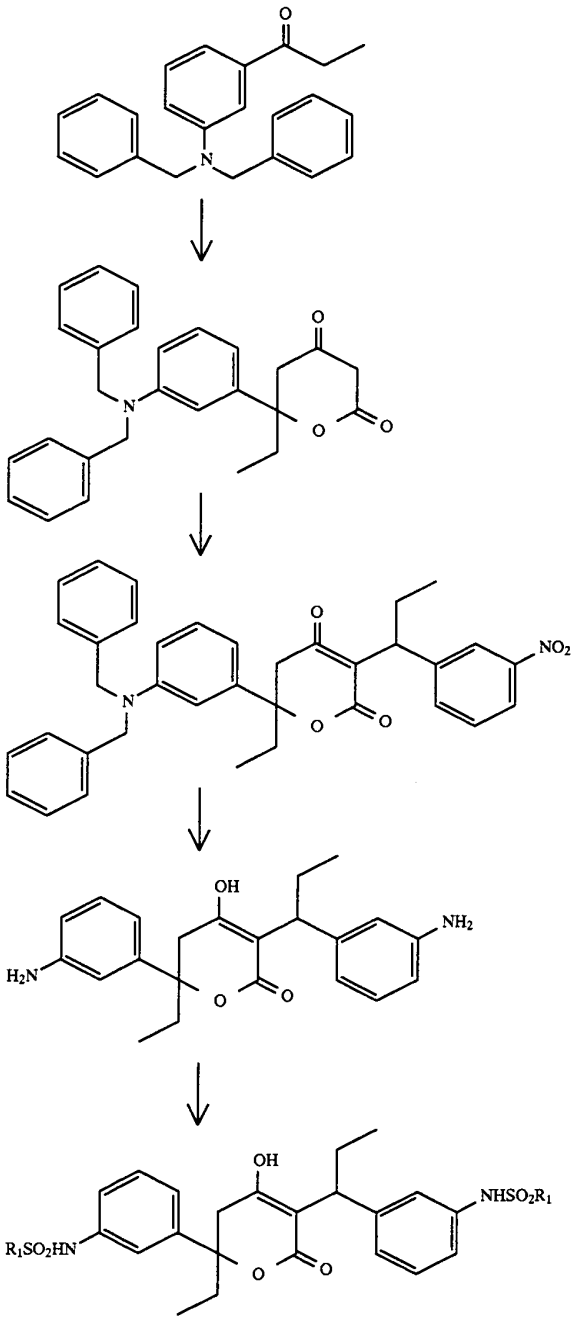

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R-4

R-5

R-6

R-7

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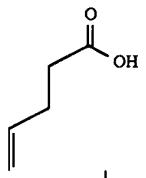

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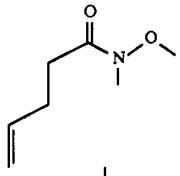

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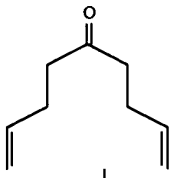

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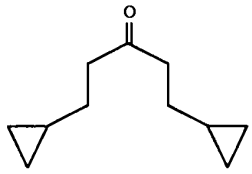

S-4 (Q-1)

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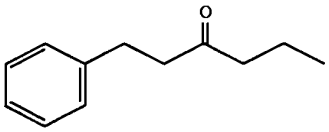

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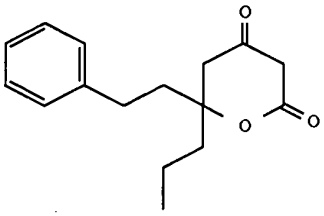

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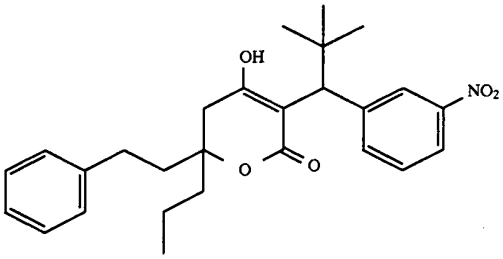

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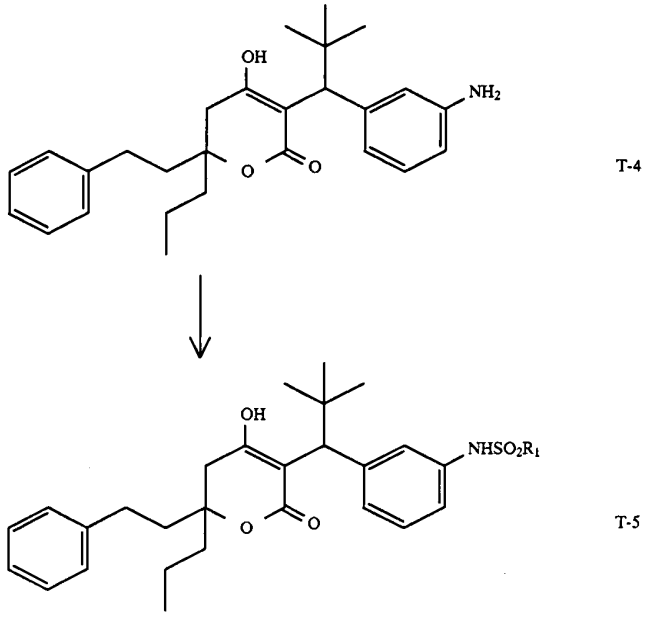
CHART T



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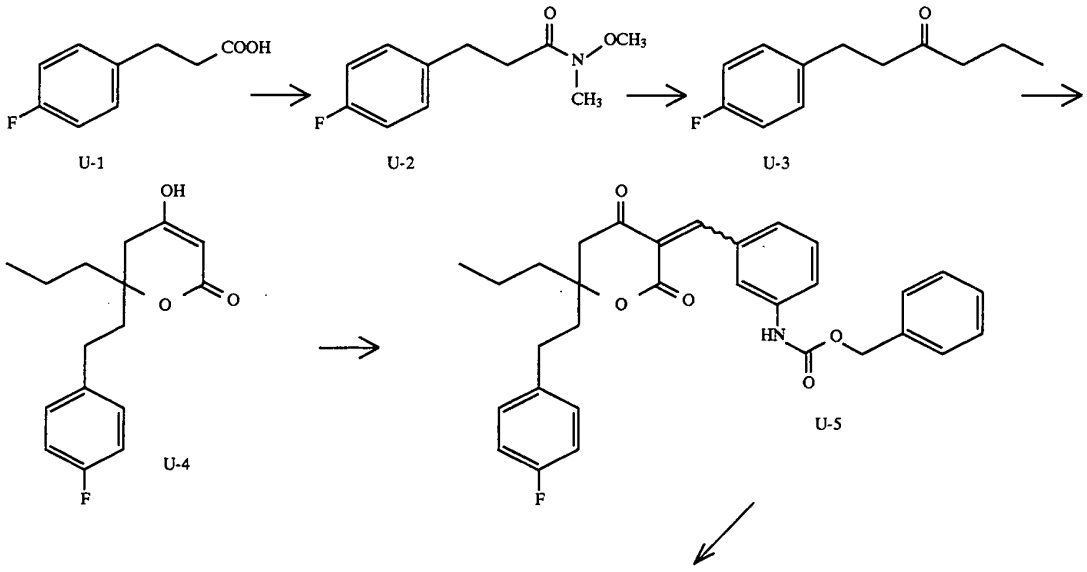

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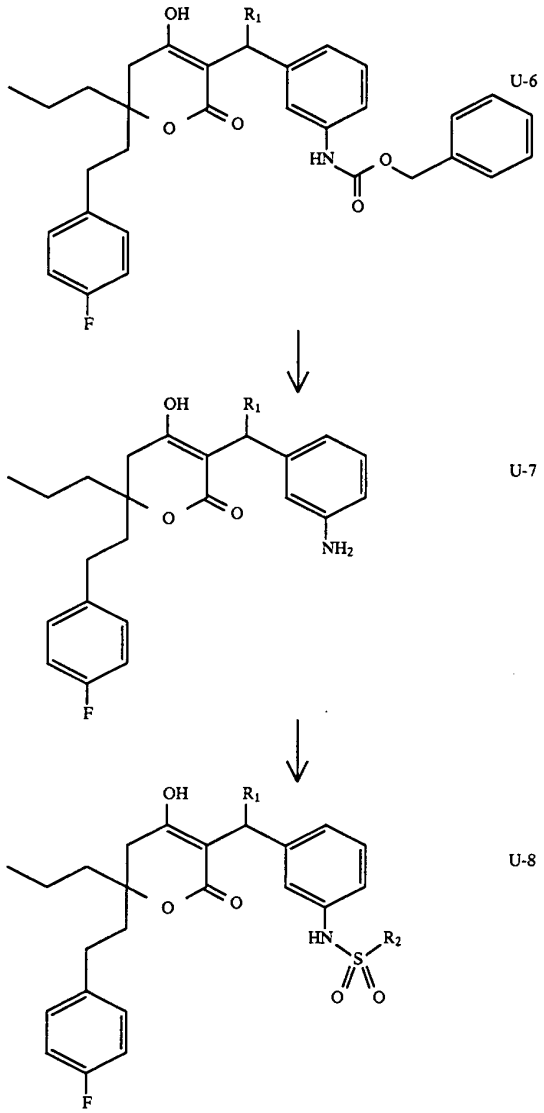

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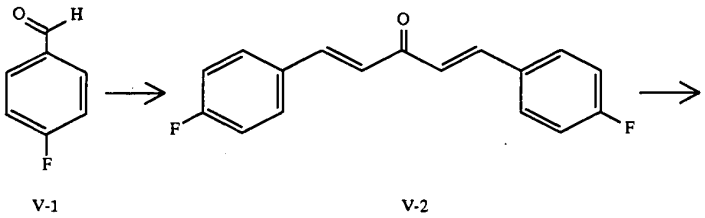

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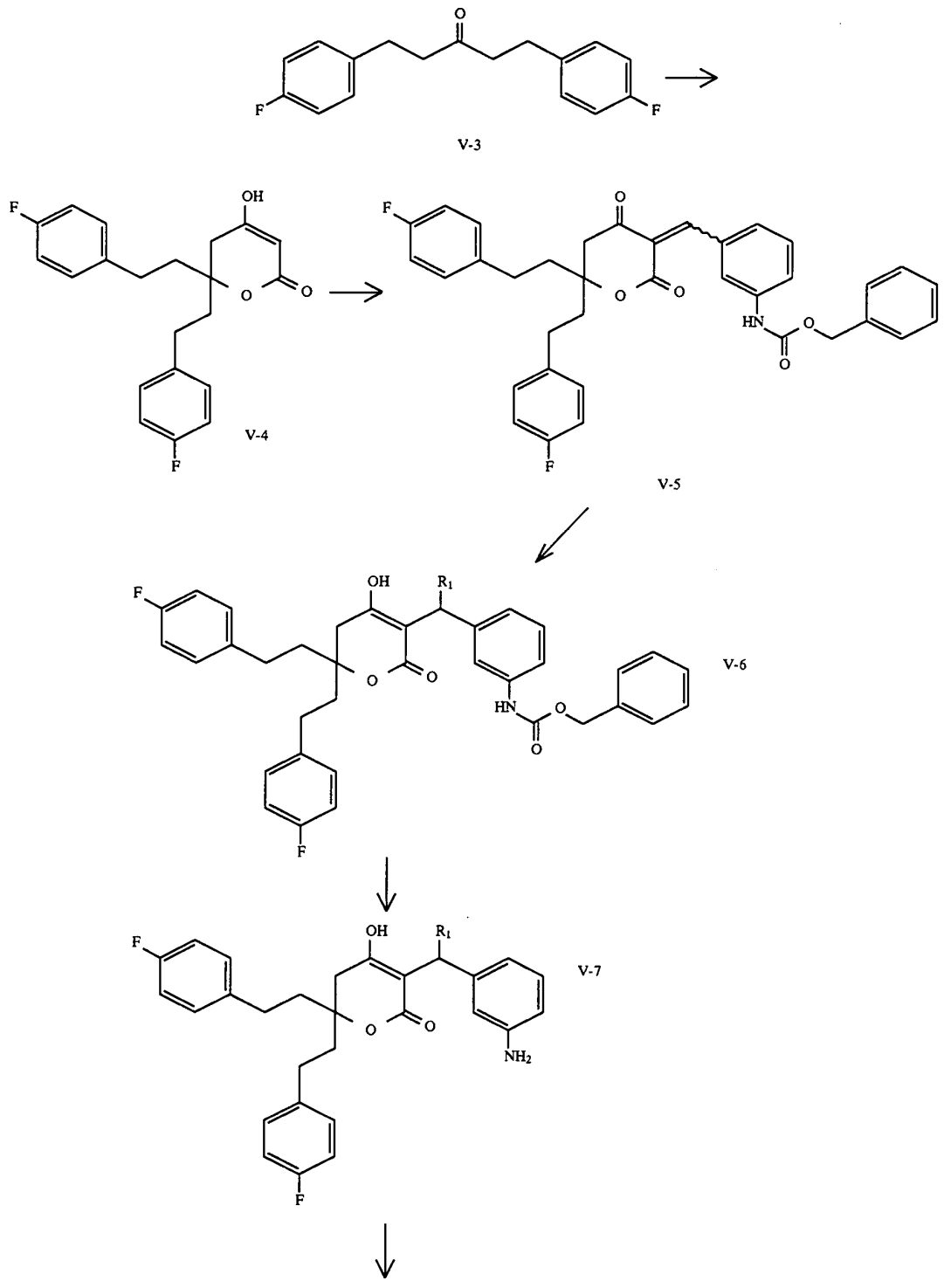

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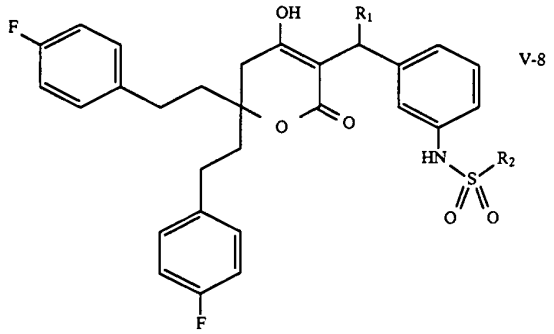

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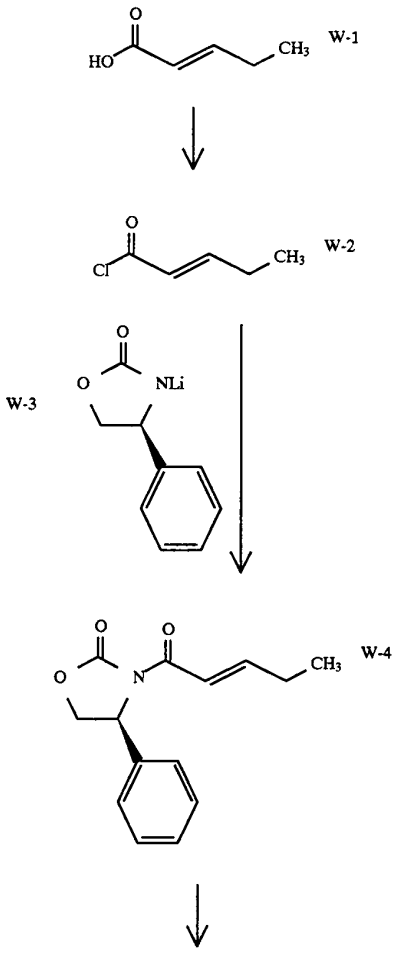

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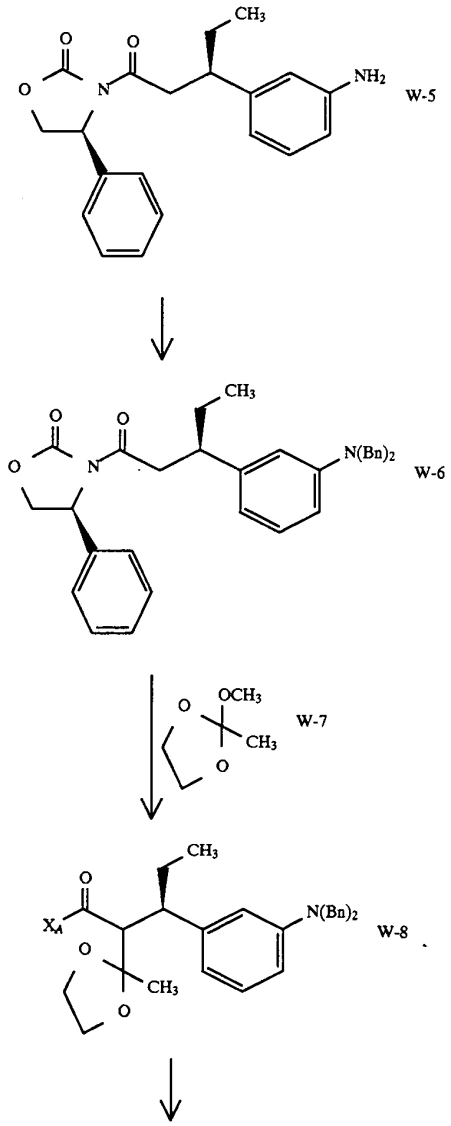

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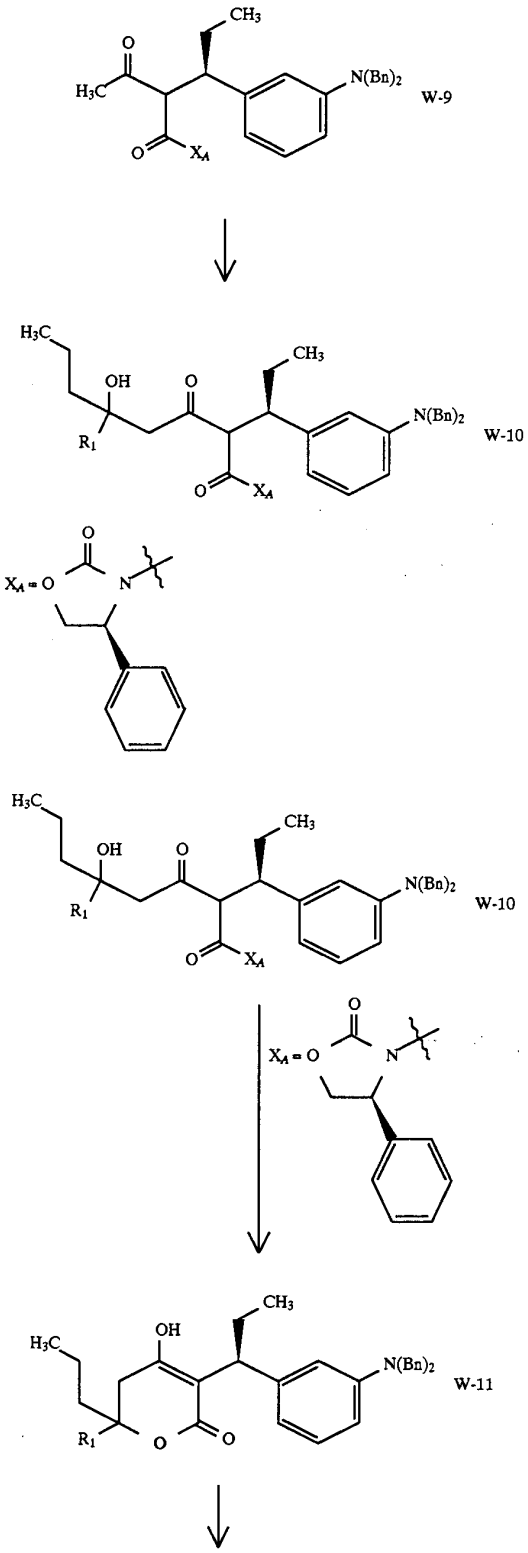

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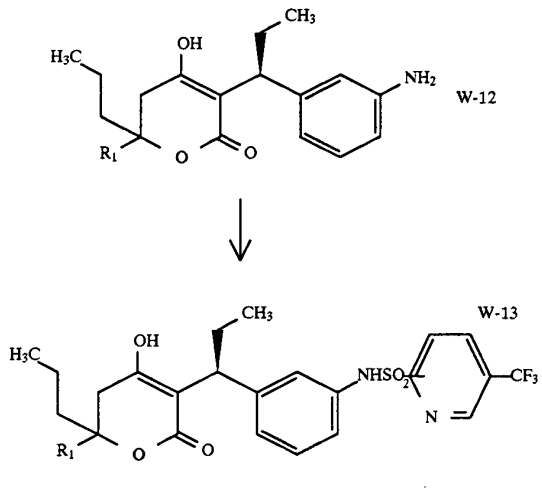

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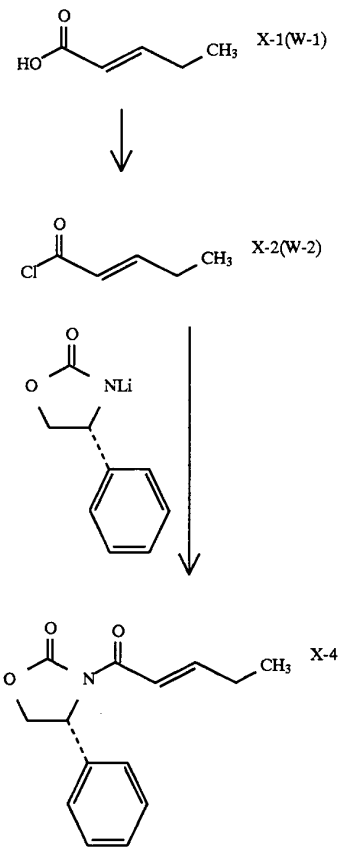

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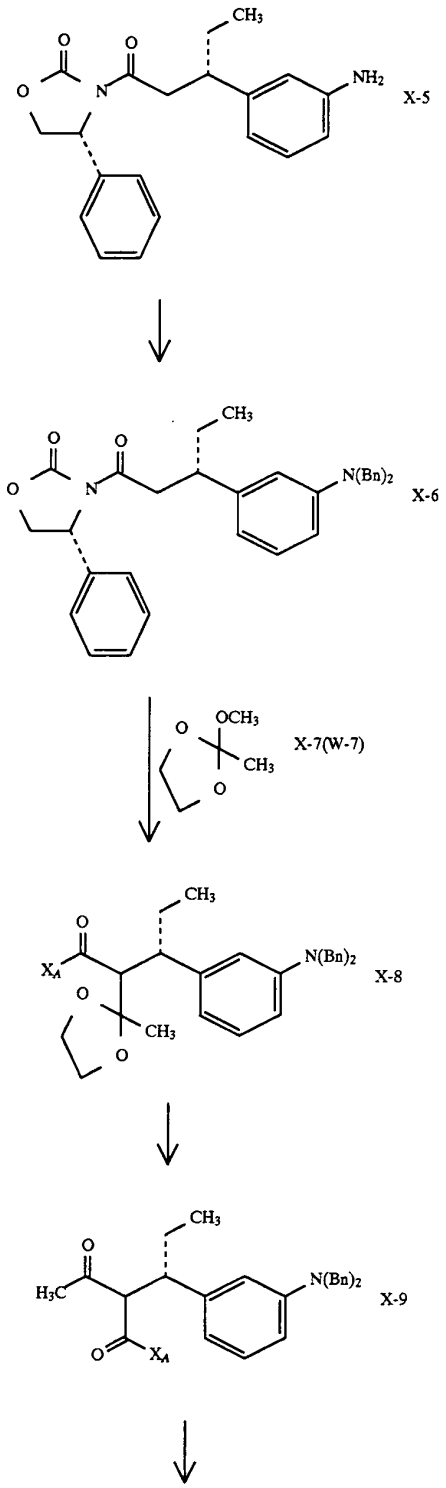

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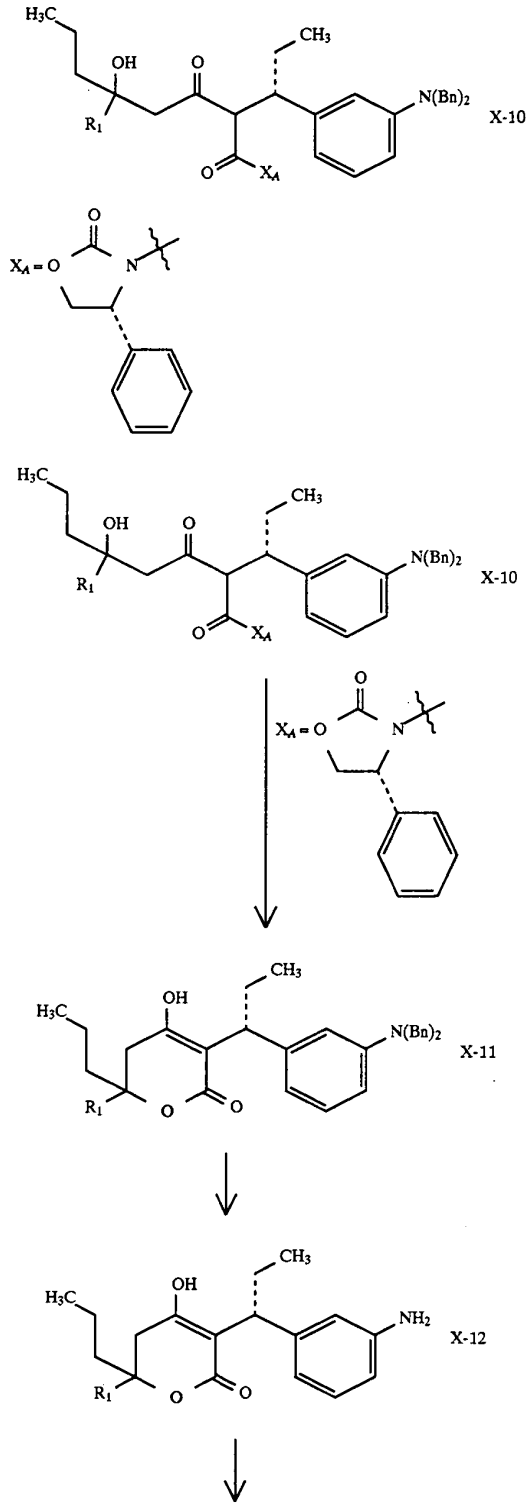

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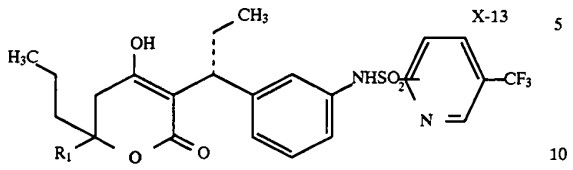

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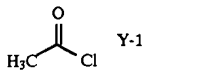

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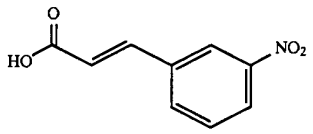

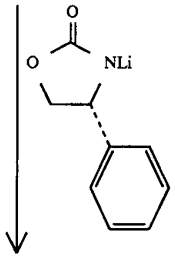

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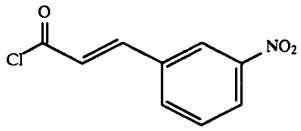
Y-7



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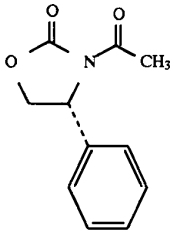

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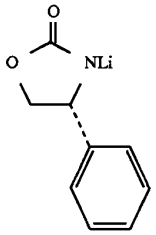

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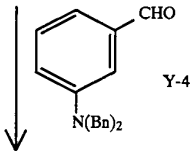

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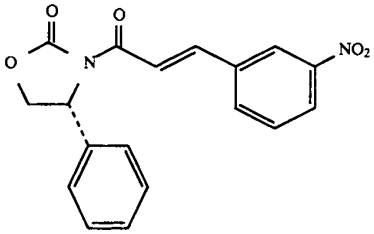

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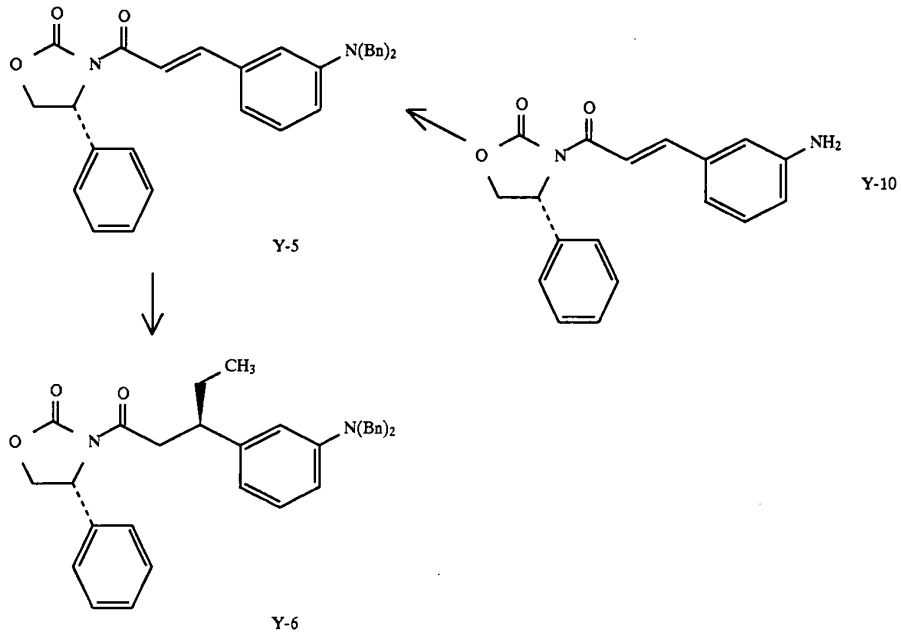

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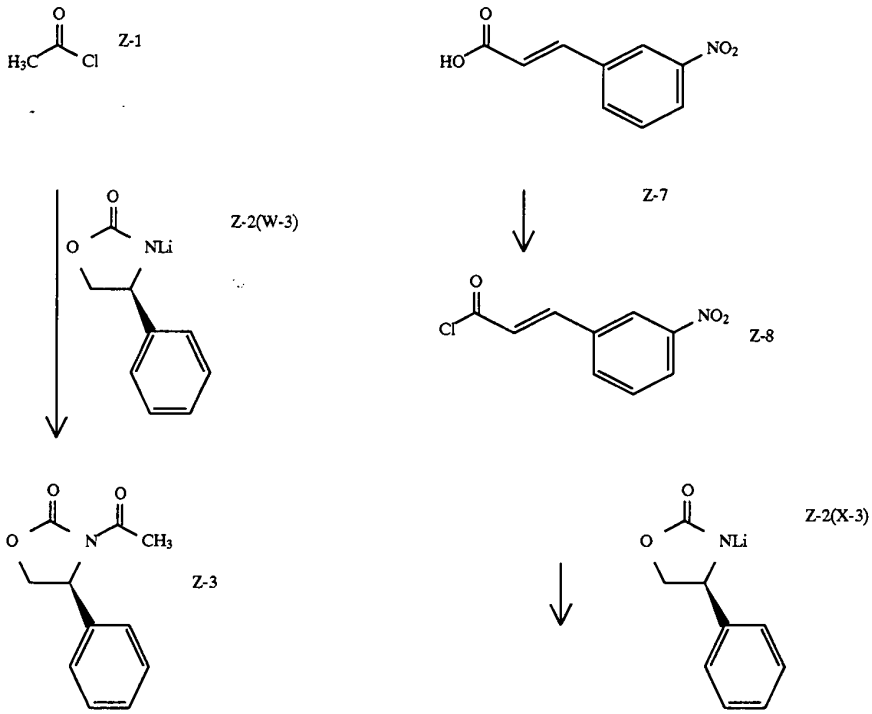

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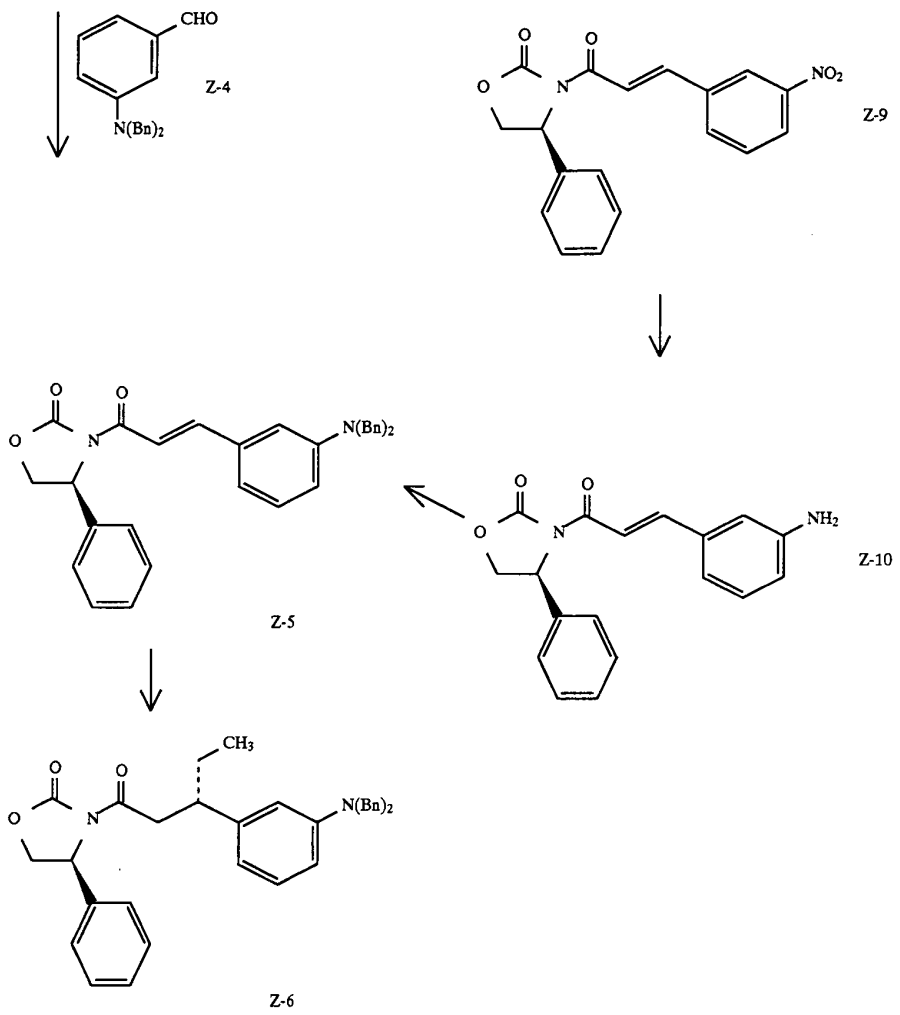

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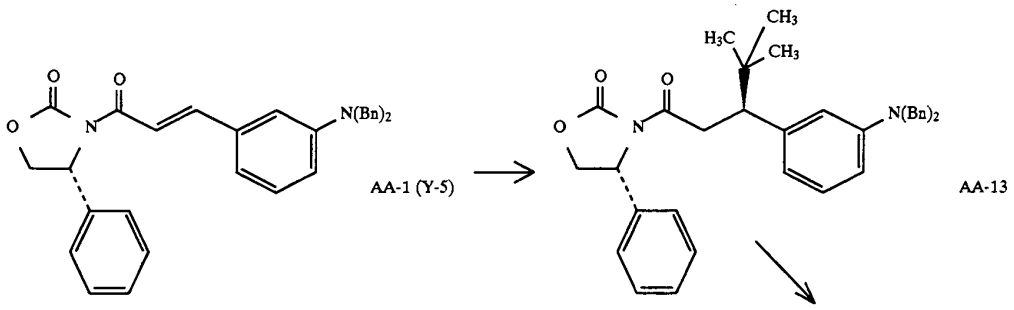

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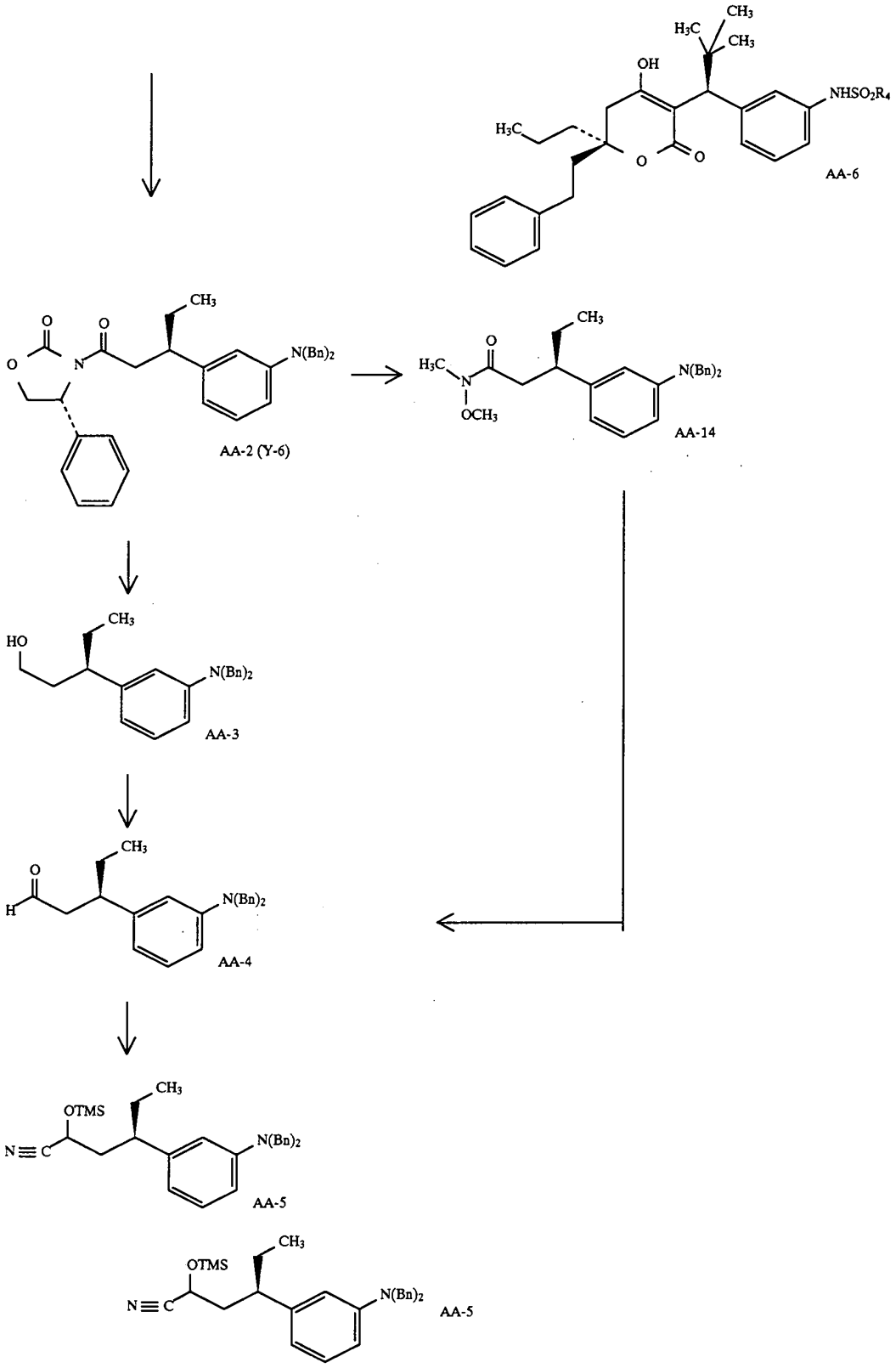

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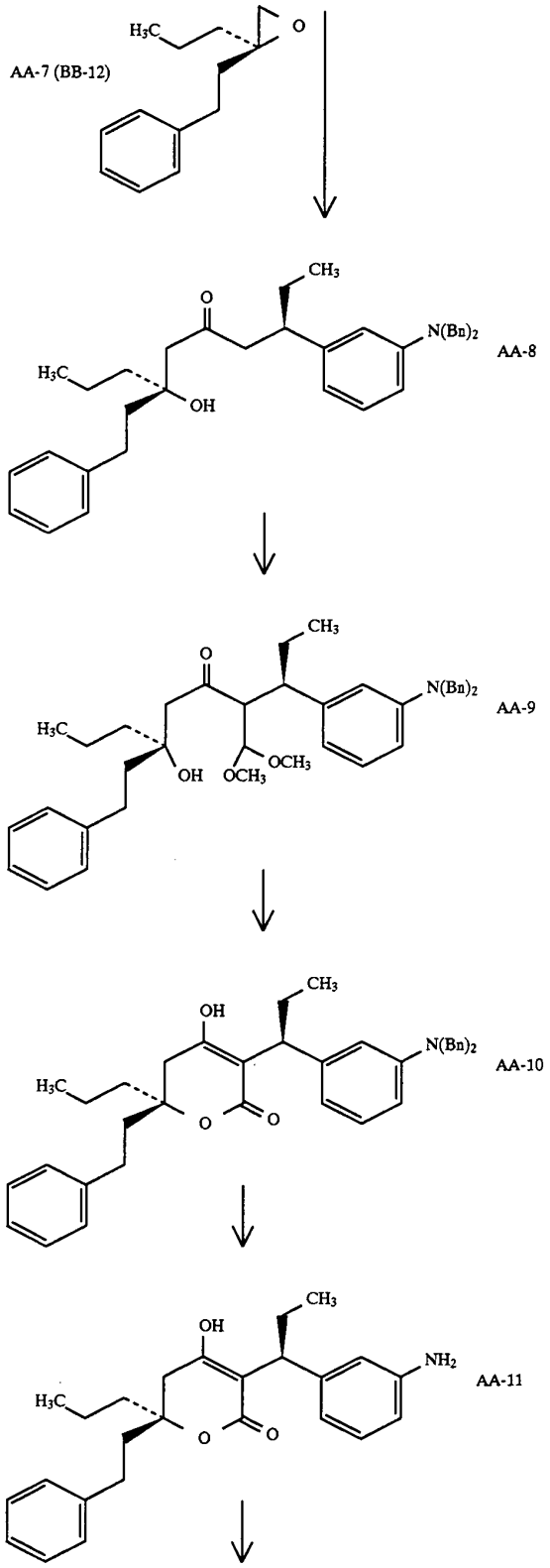

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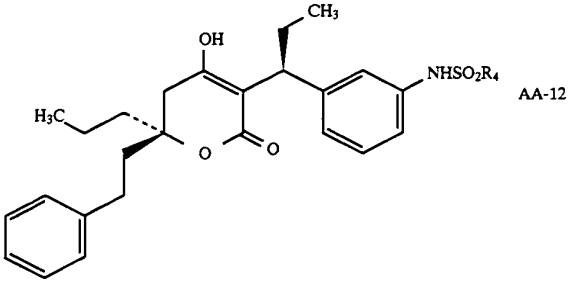
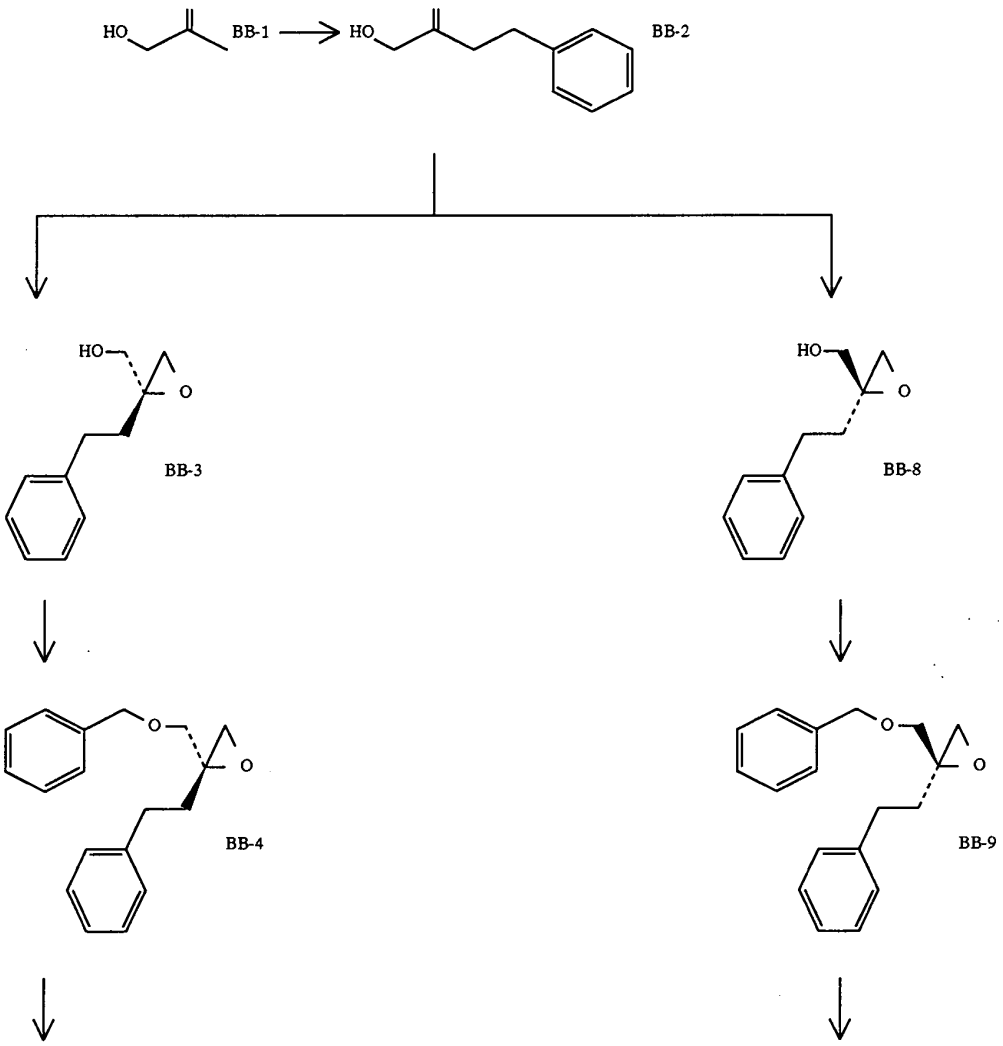


AA-12

CHART BB



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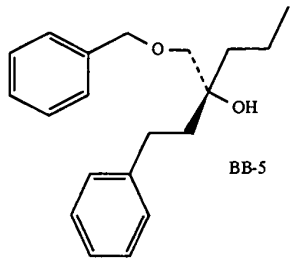

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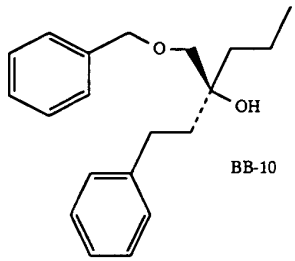
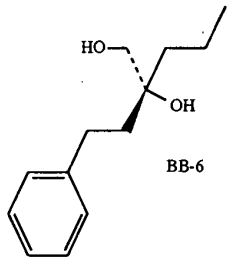


BB-10



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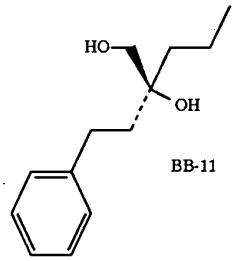

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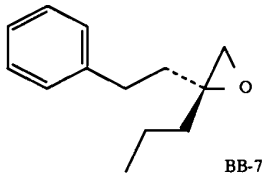

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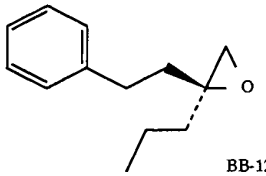

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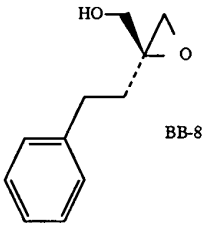

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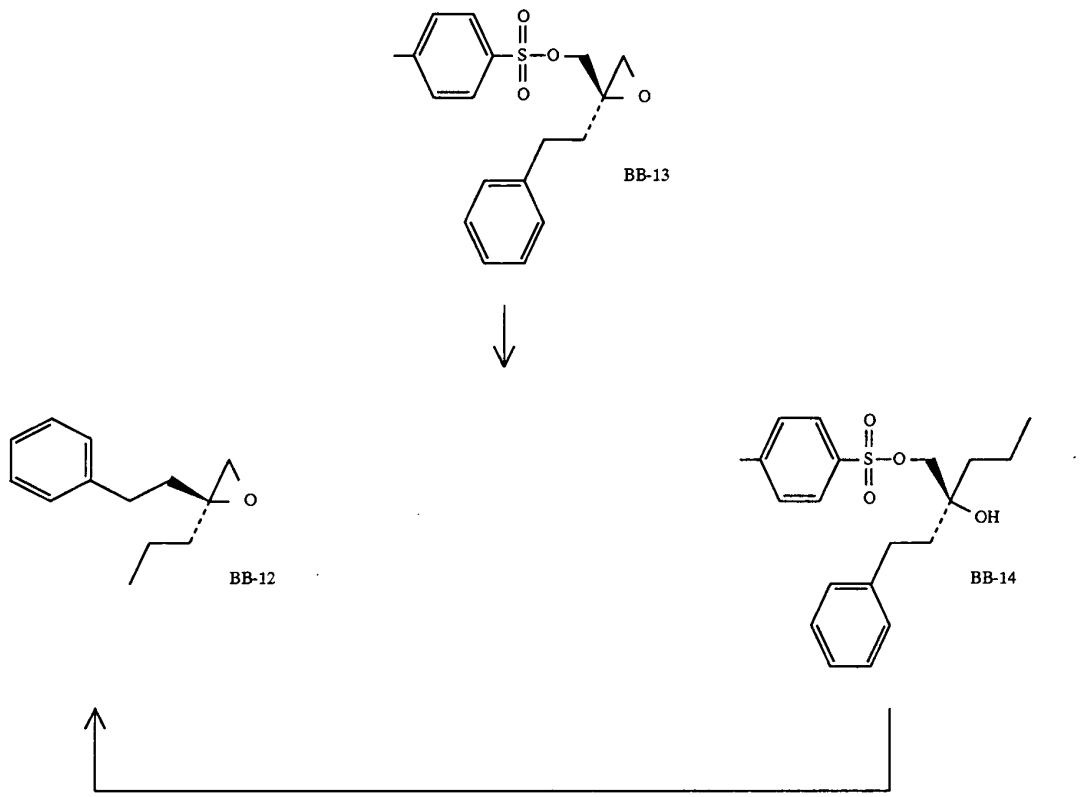

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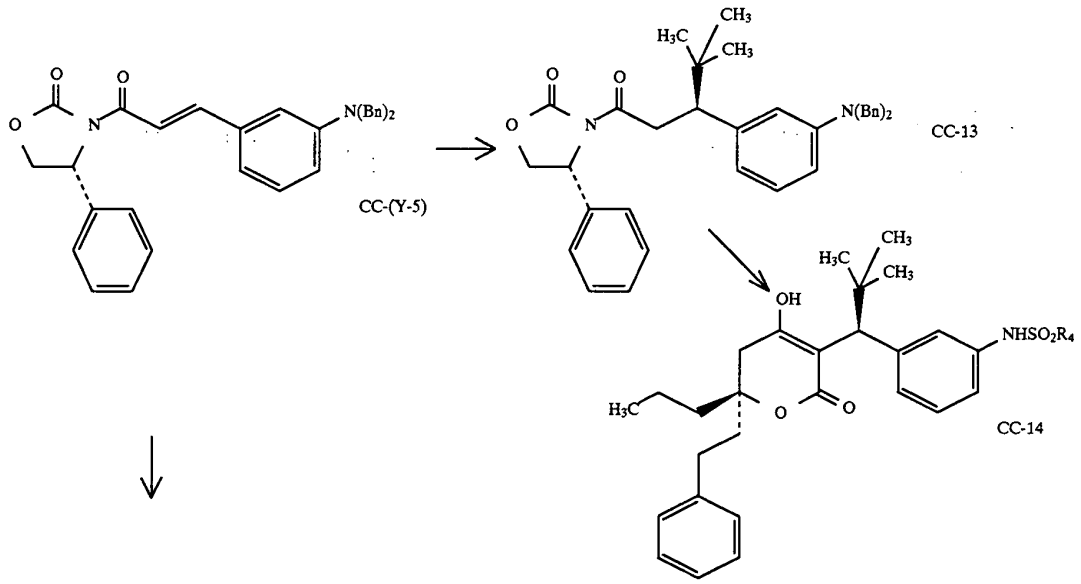

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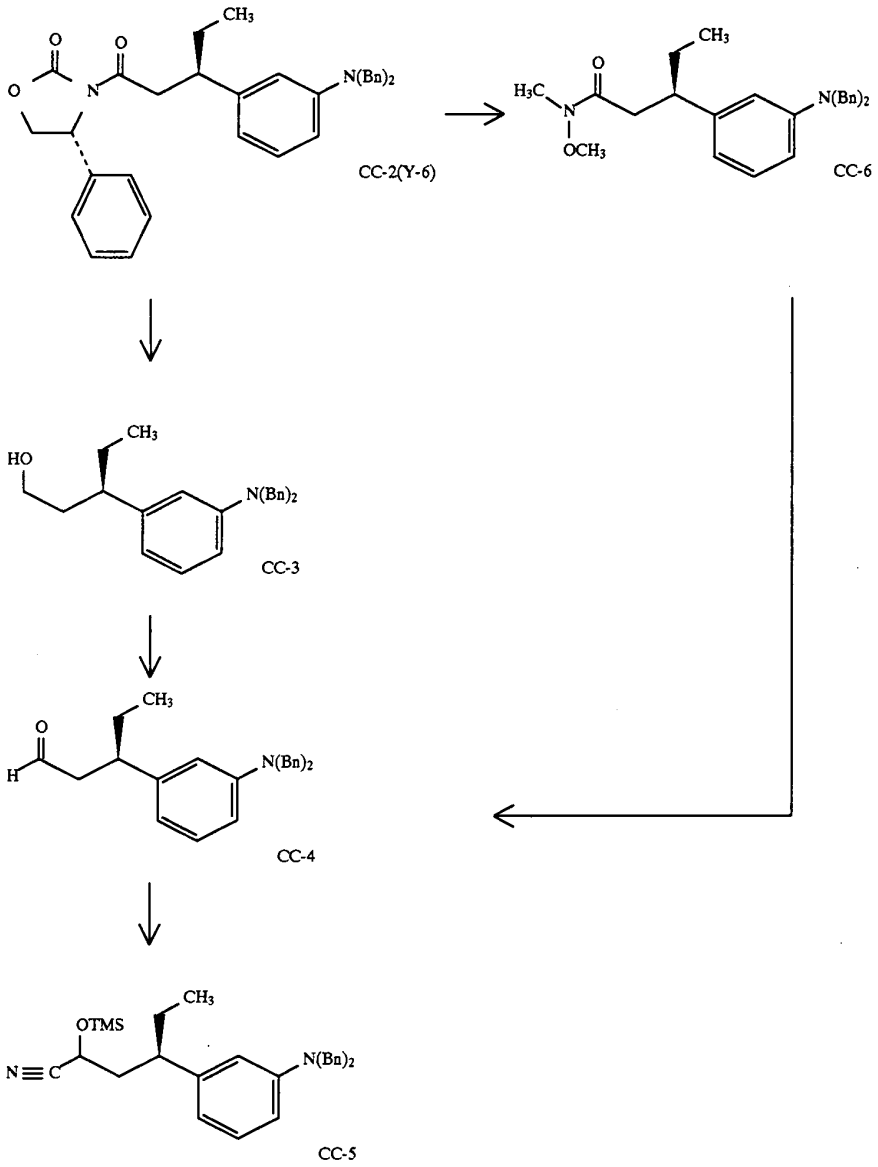

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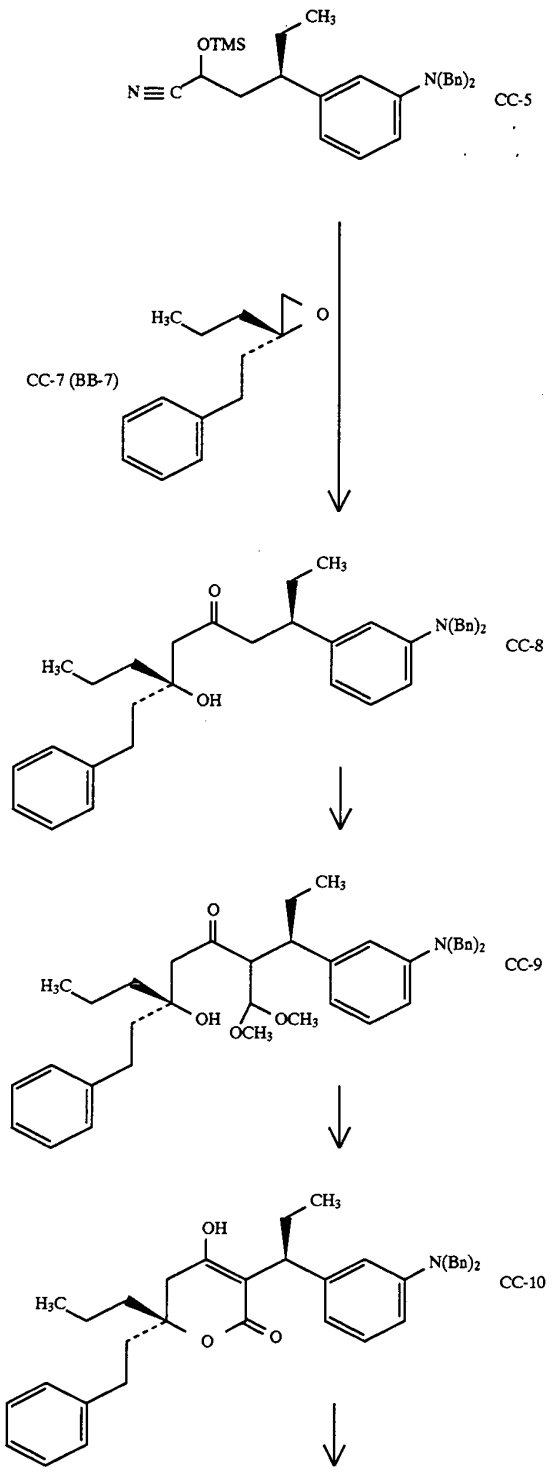

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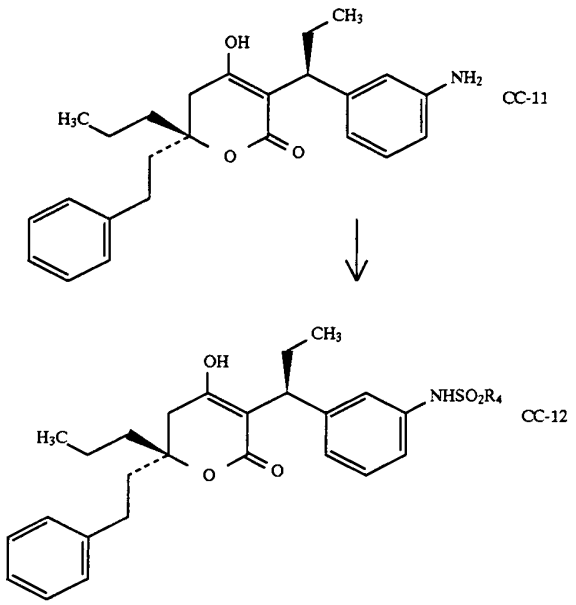

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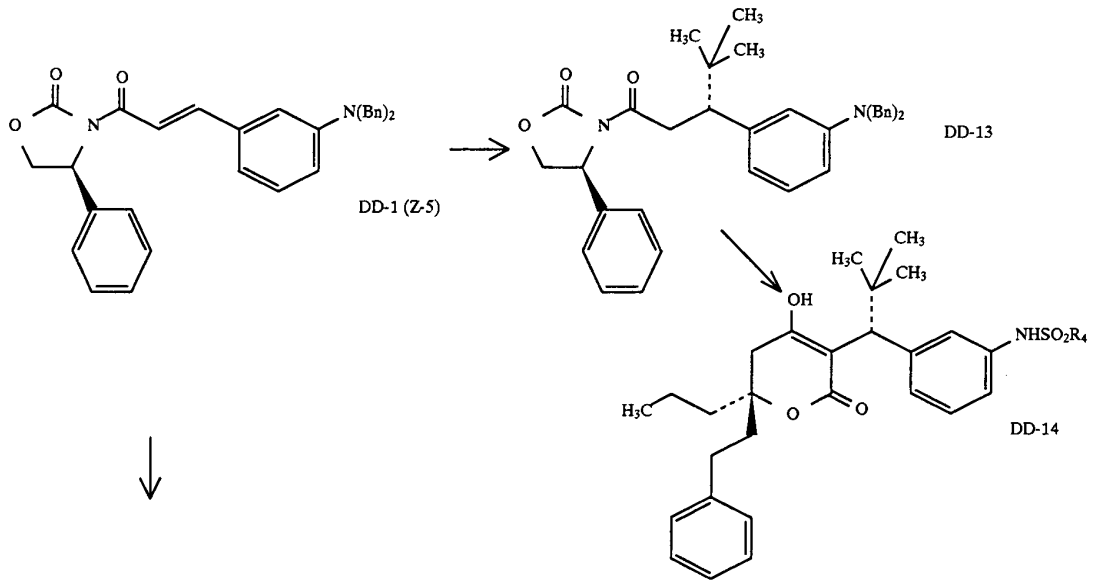

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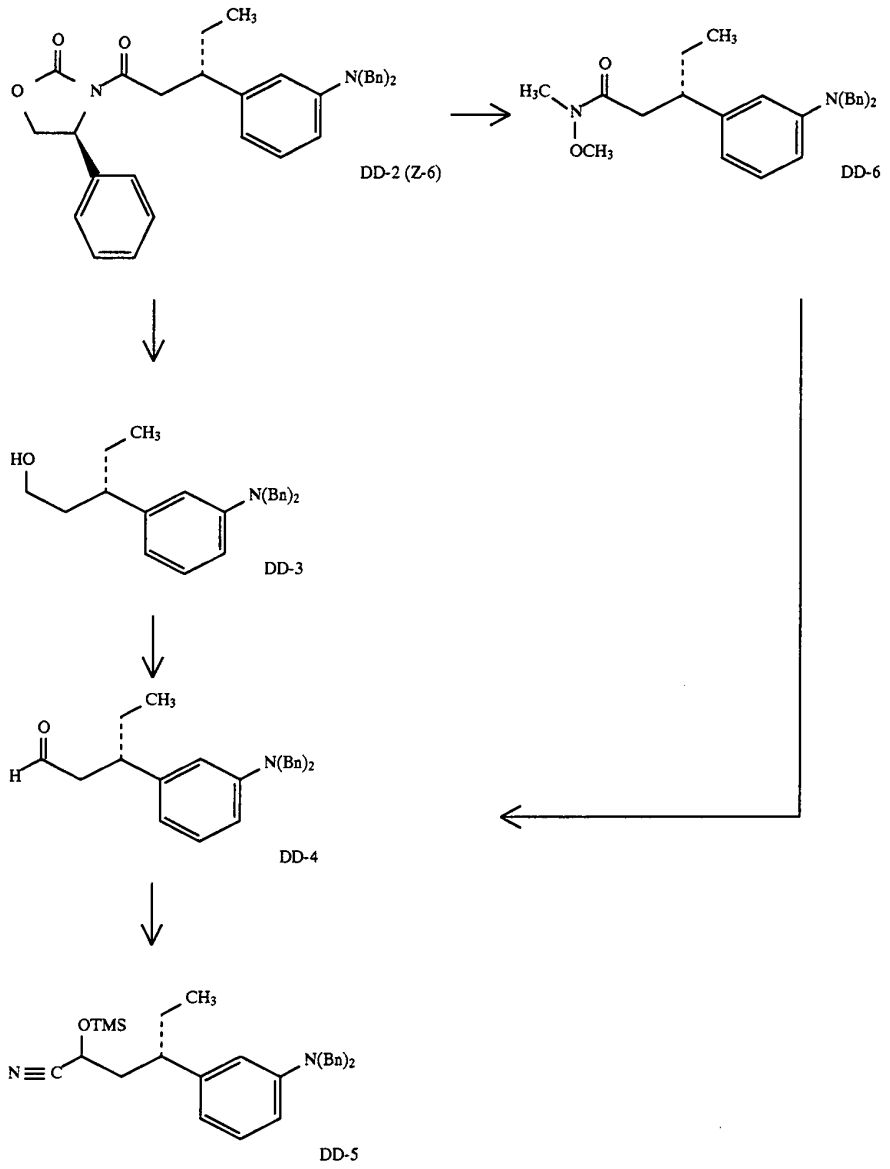

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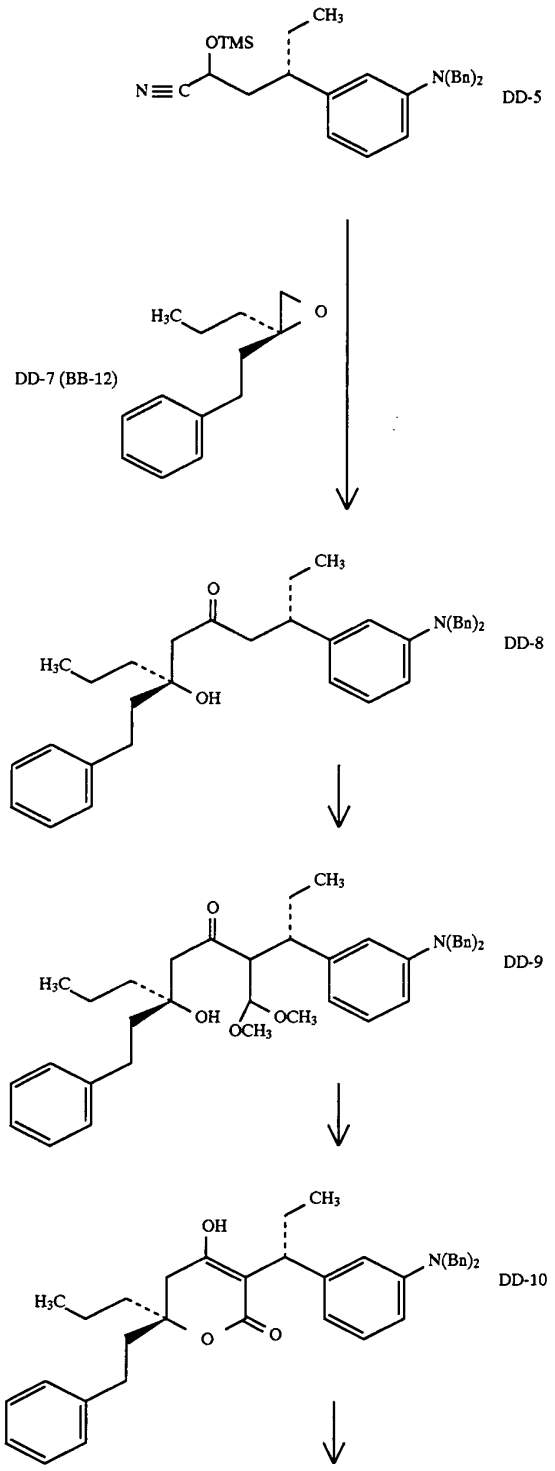

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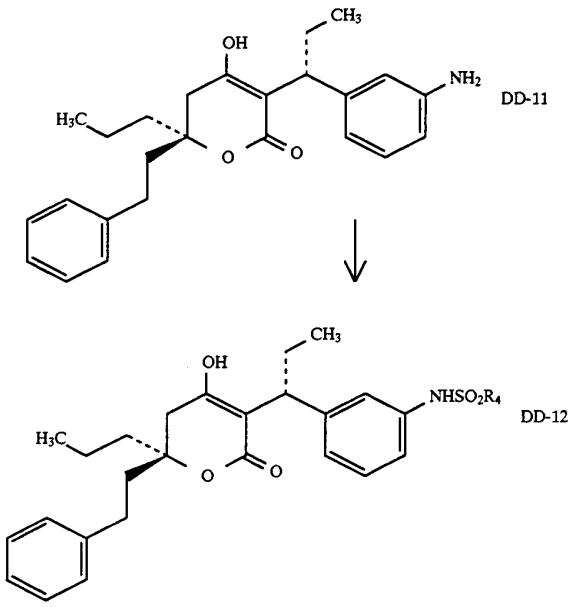

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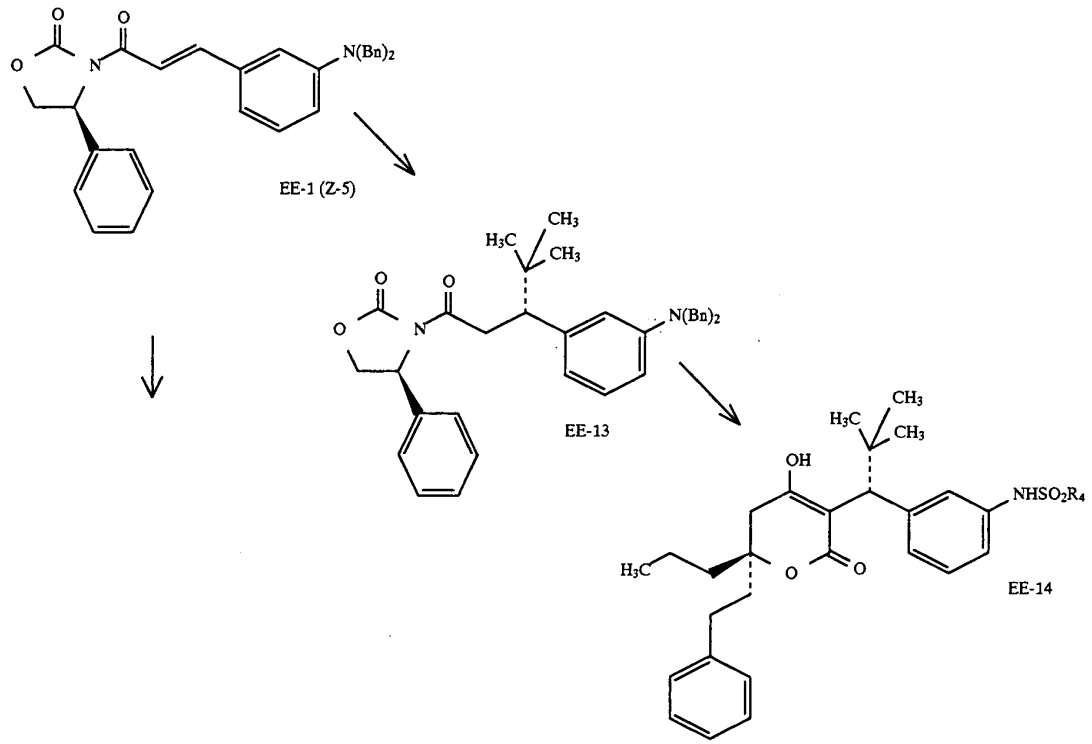

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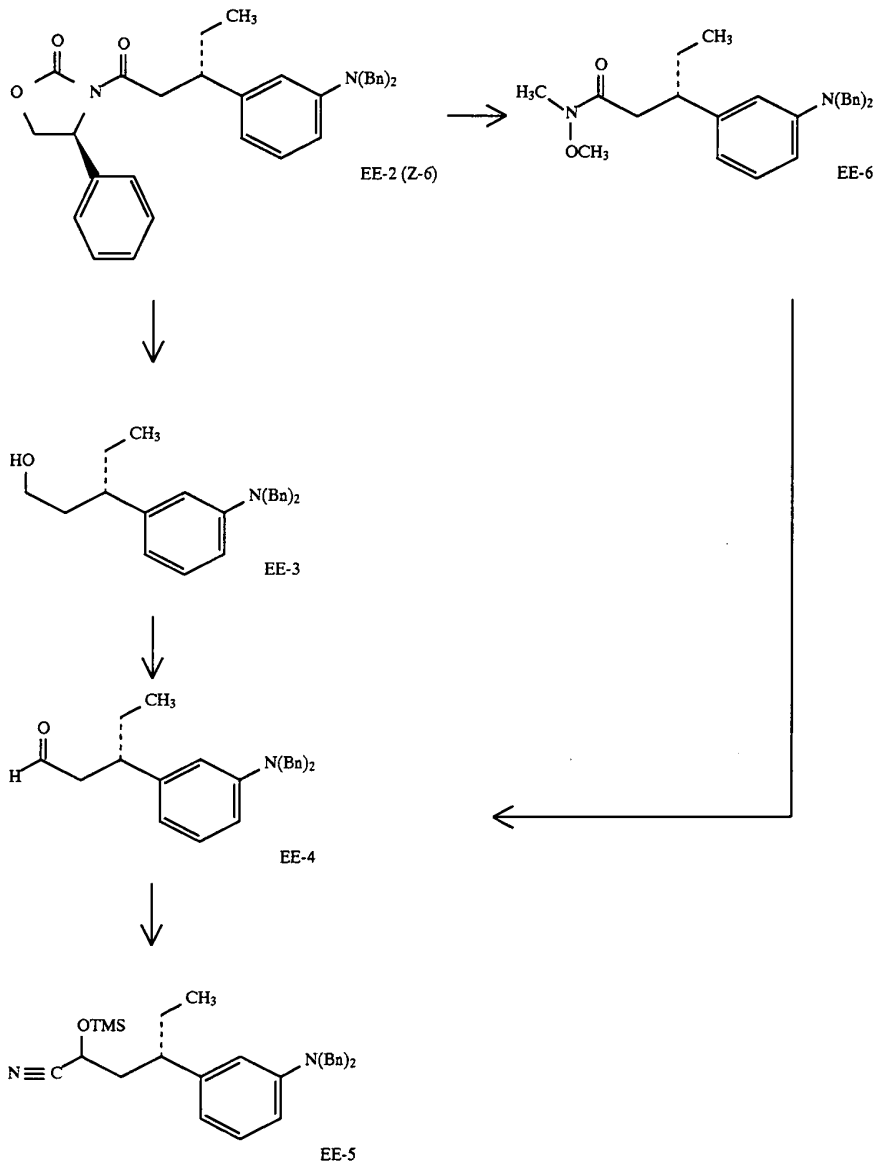

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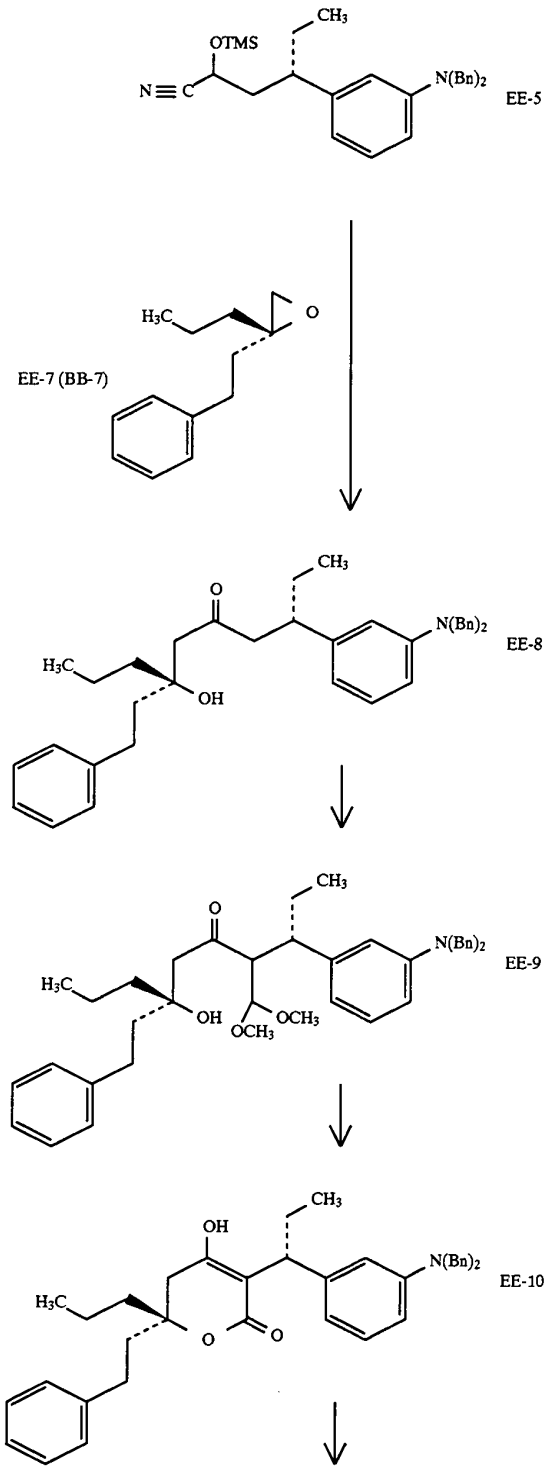

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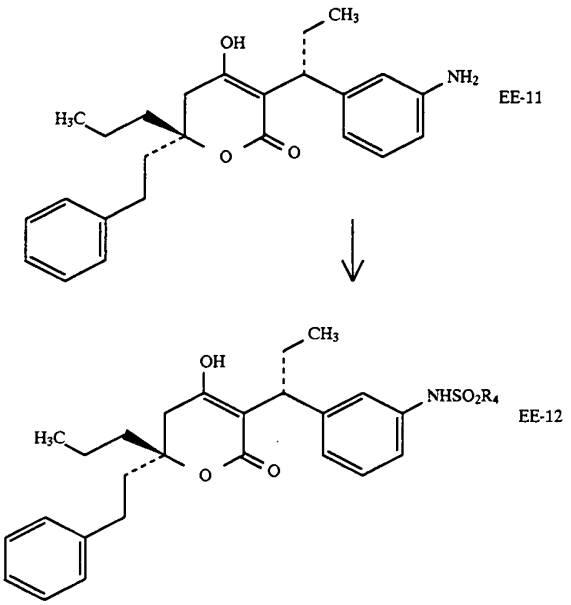

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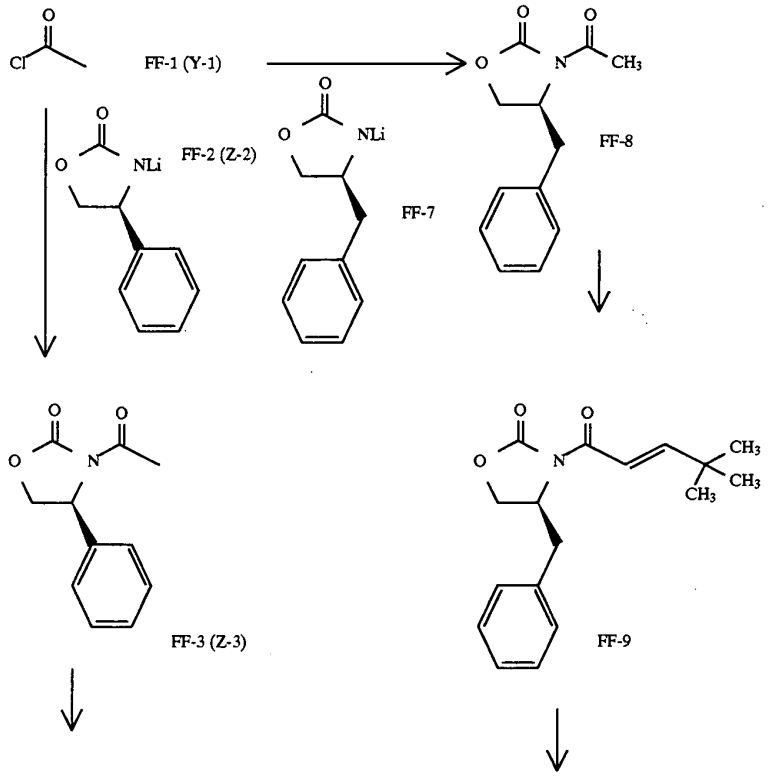

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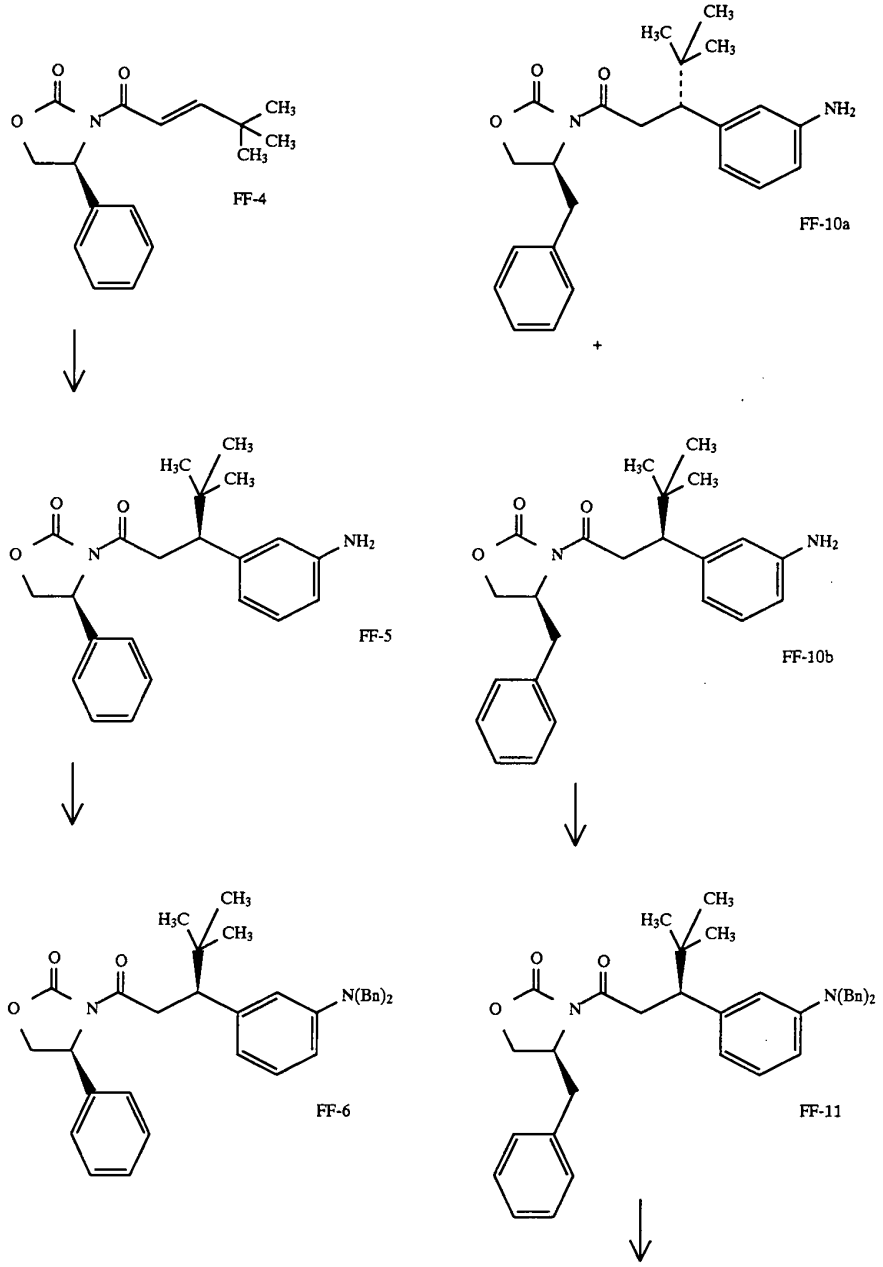

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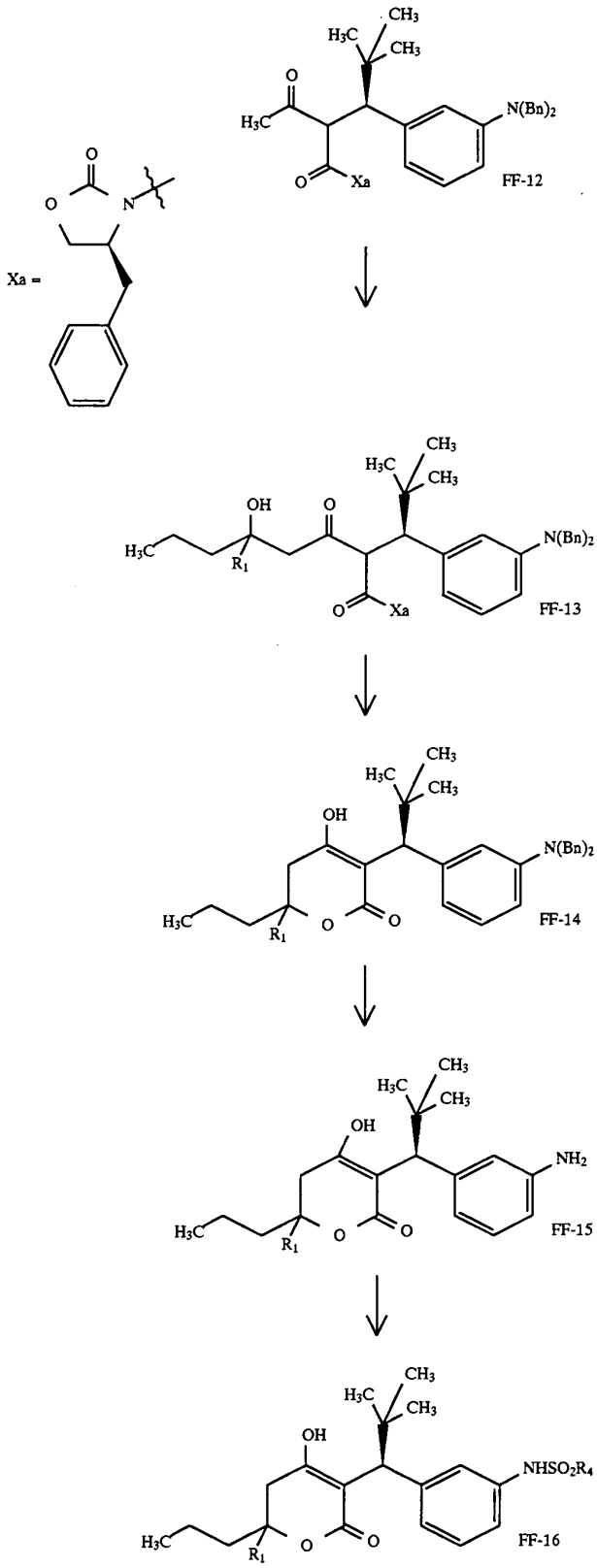

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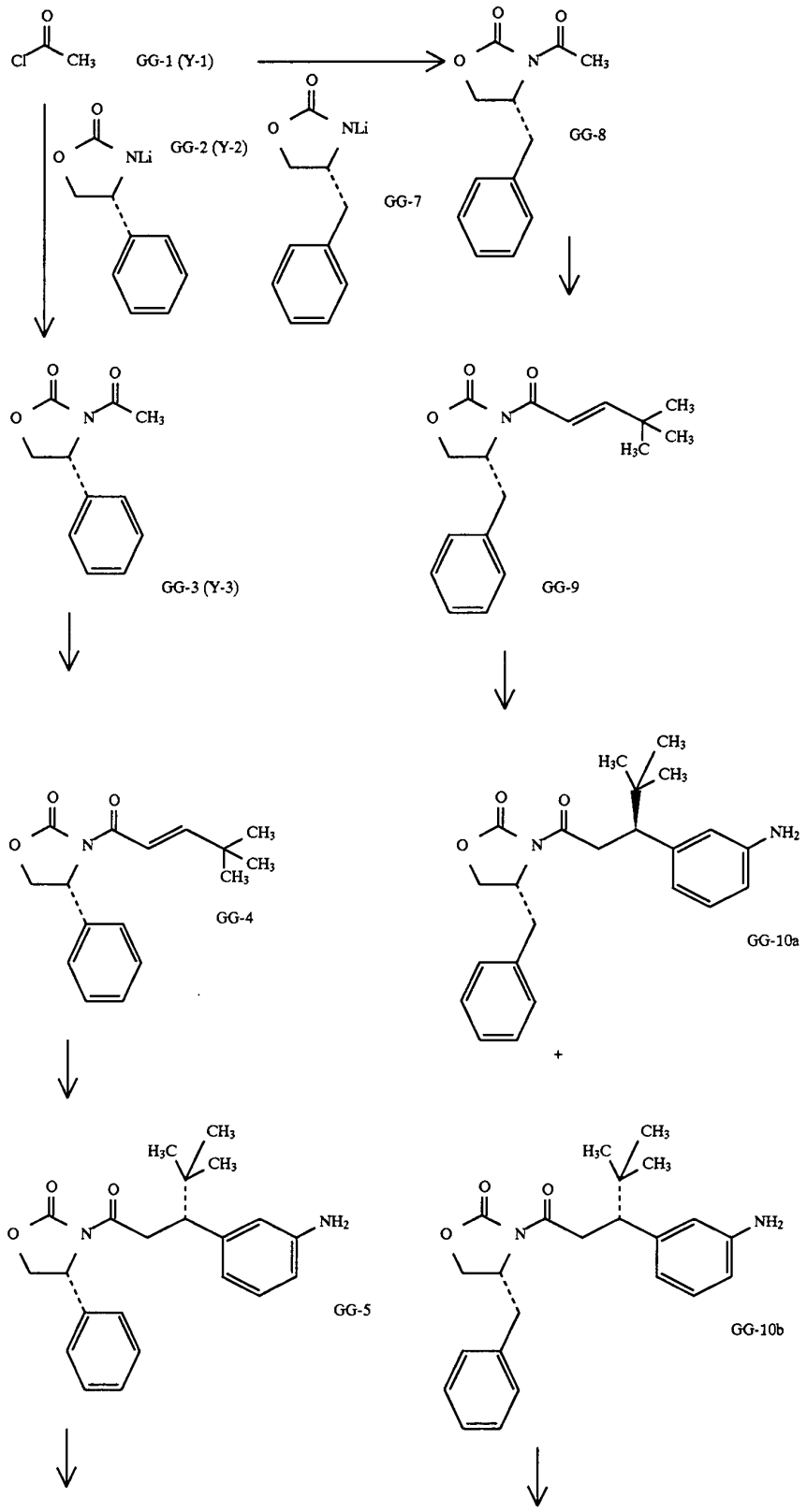

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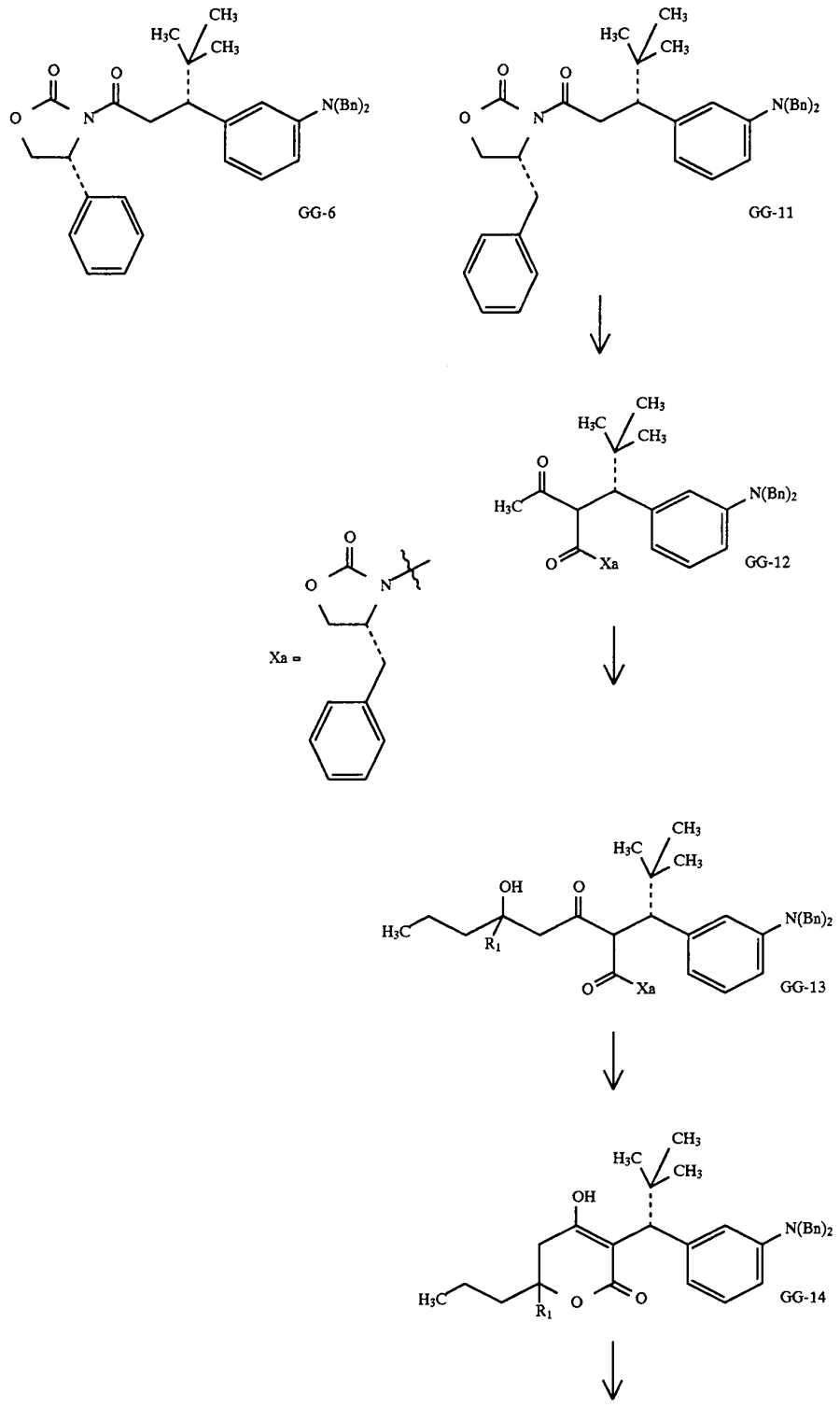

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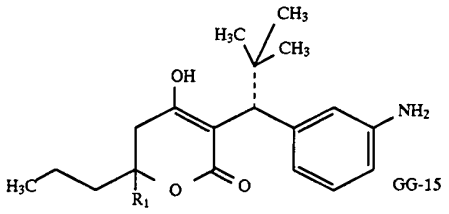

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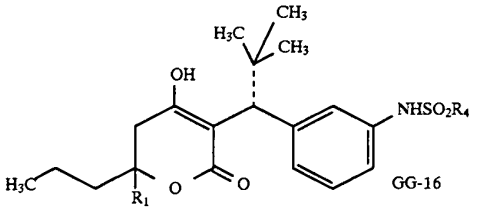

GG-16

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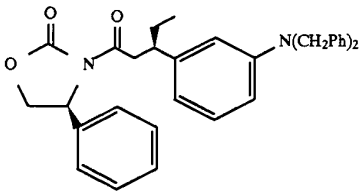
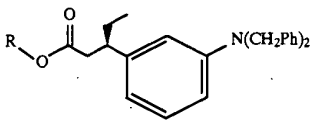


HH-1 (W-6)



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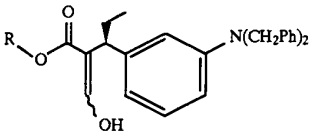

HH-3

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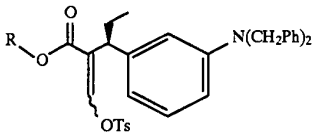

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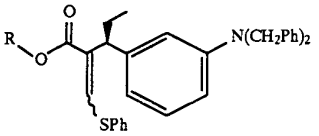

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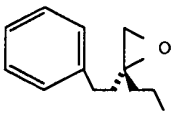
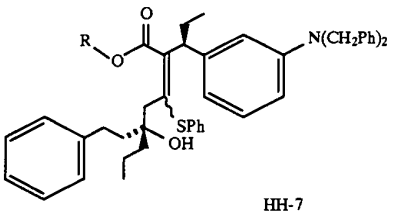


HH-6 (BB-7)



HH-7

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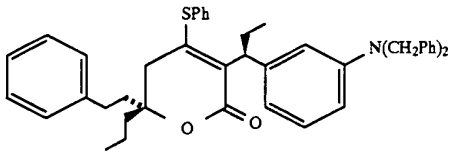
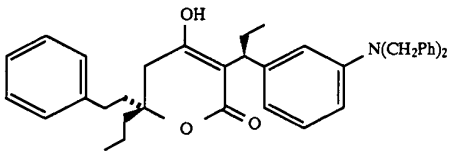
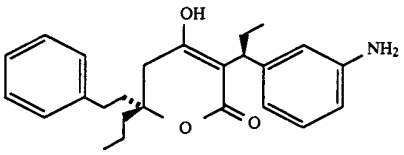
CHART HH



HH-8



HH-9



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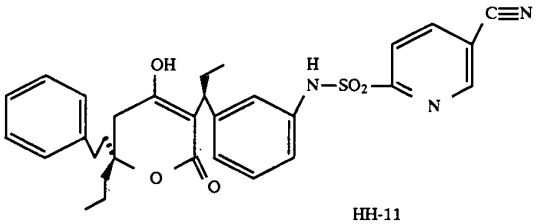
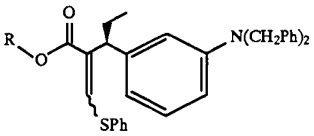
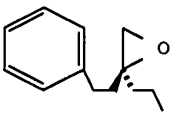


HH-11

CHART II



II-5 (HH-5)



II-2 (BB-12)

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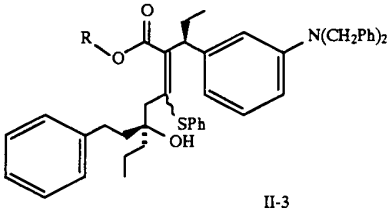
CHART II



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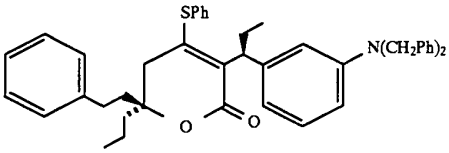

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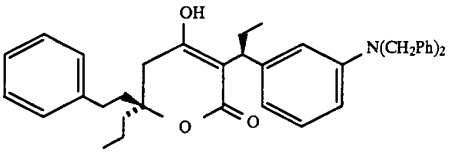

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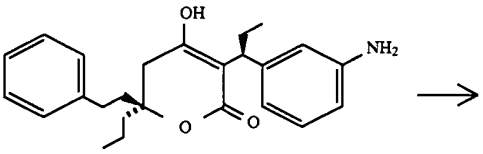

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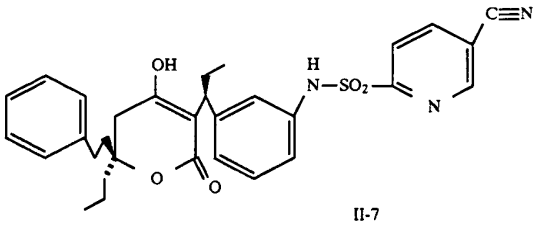
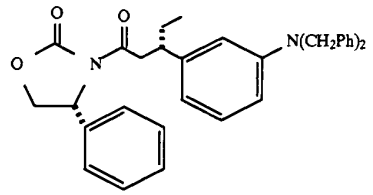
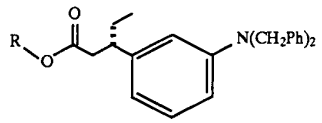


II-7

CHART JJ



JJ-1 (X-6)



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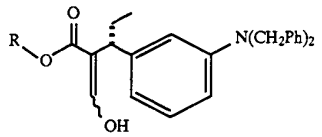

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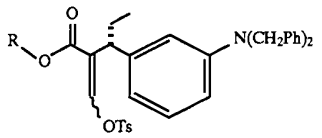

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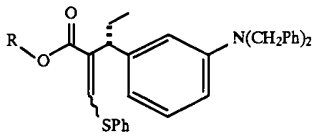

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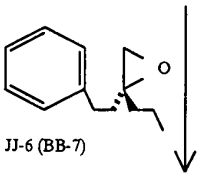

JJ-6 (BB-7)

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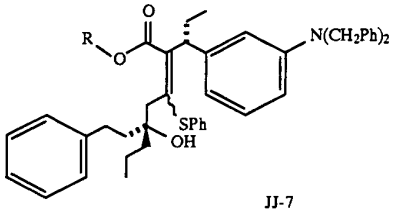
CHART JJ



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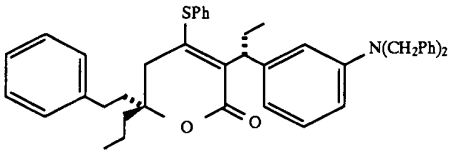

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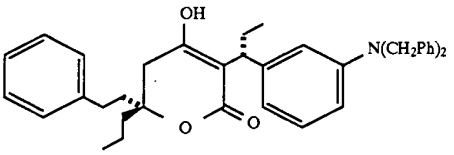
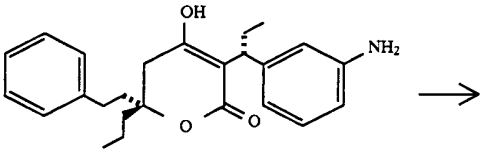


JJ-9



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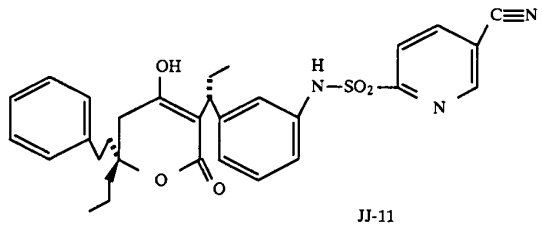
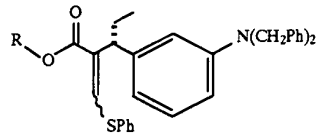


JJ-11

CHART KK



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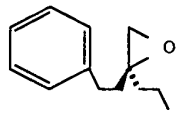
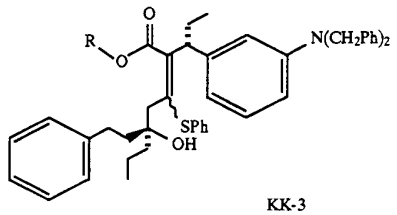


KK-6 (BB-12)



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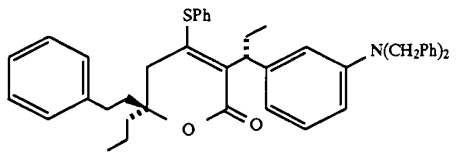

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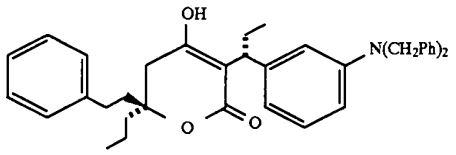
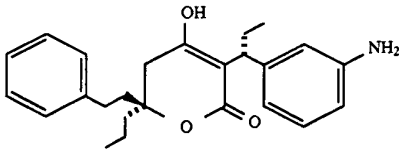


KK-5



KK-6

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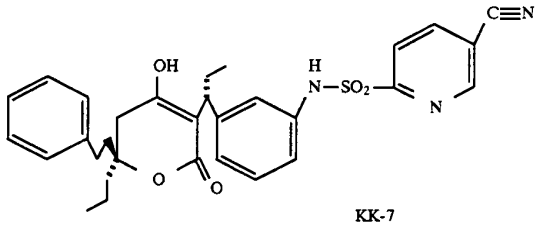

KK-7

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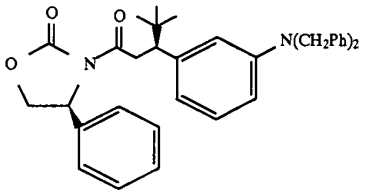

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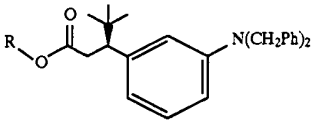

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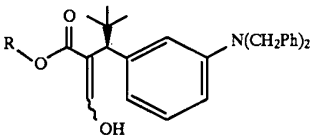

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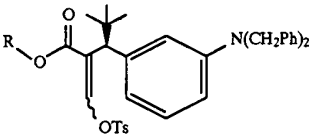

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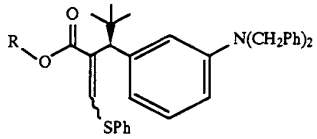

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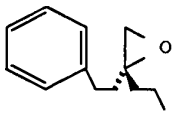

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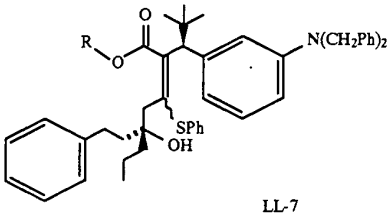

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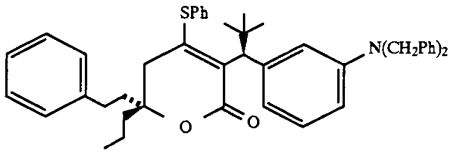

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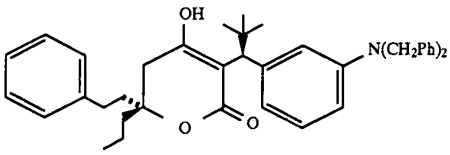

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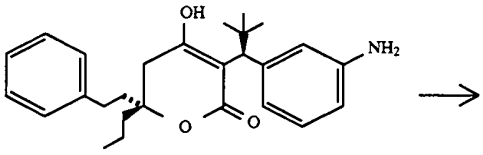

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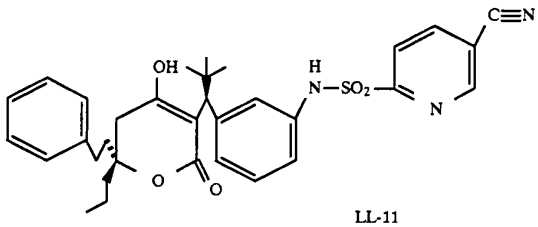

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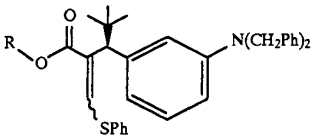

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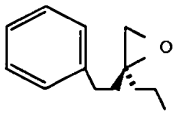

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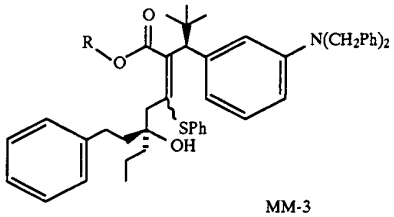

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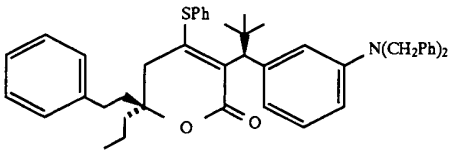

MM-4

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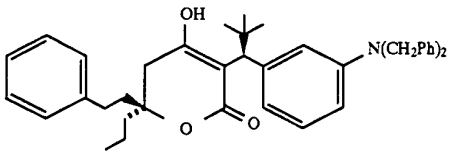

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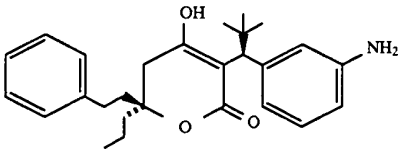

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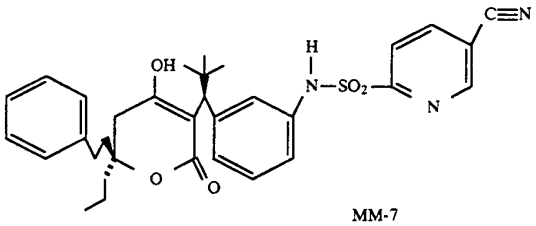

MM-7

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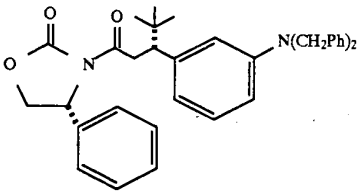

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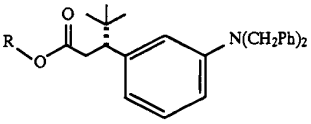

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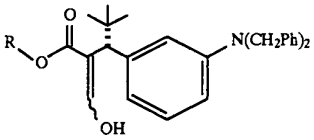

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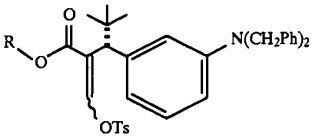

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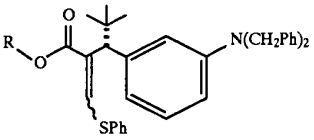

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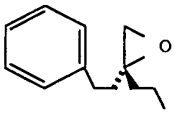

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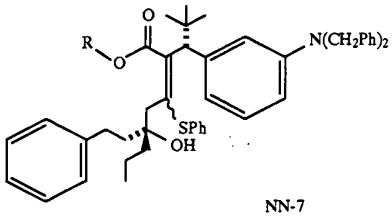

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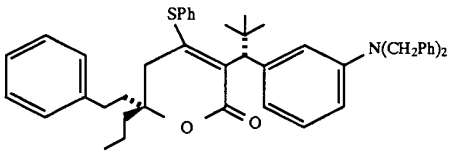

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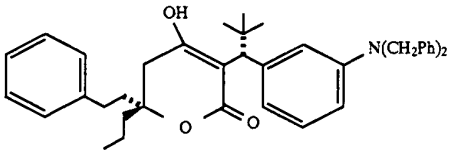

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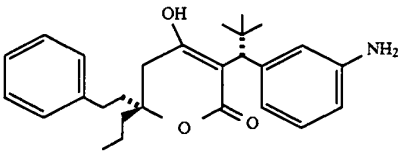

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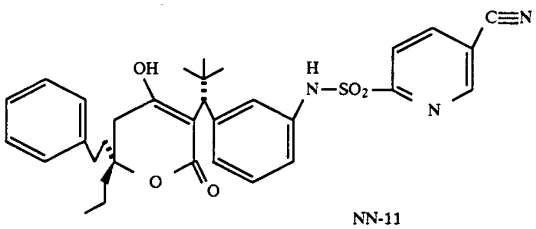

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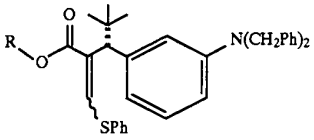

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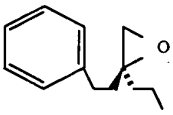

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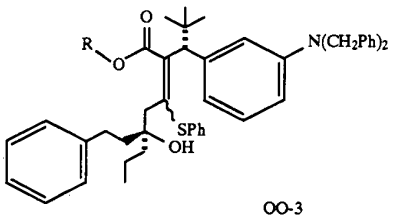

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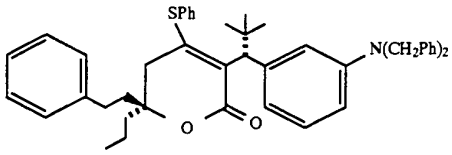

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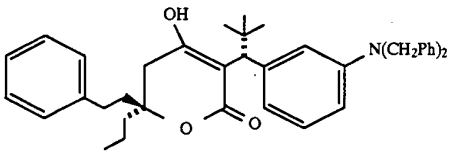

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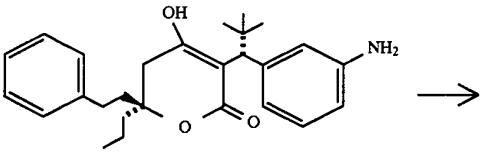

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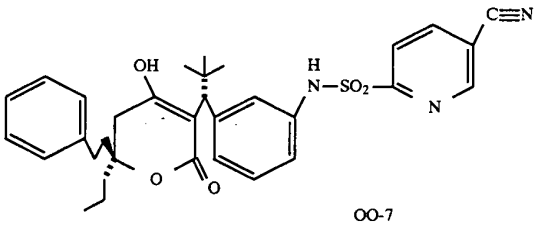

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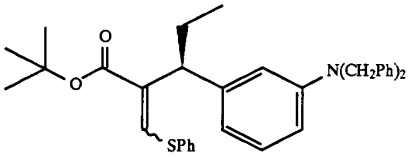
CHART PP



PP-1 (HH-5)

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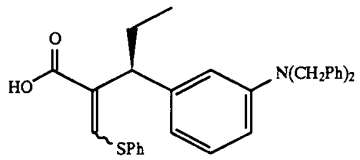
CHART PP



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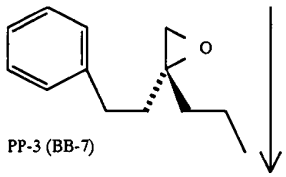

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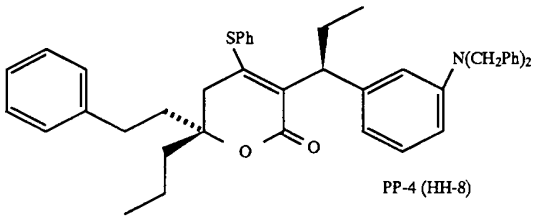

PP-4 (HH-8)

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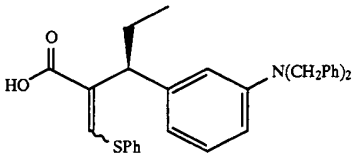

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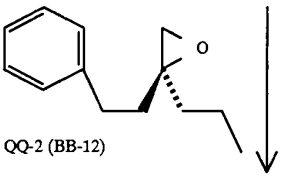

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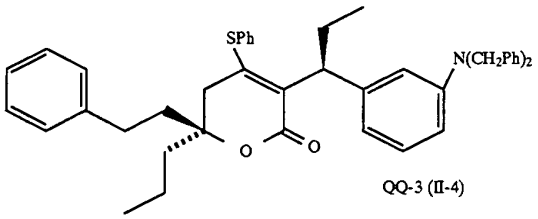

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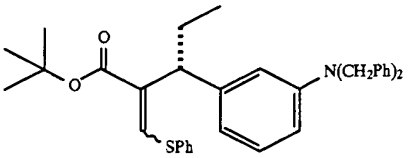

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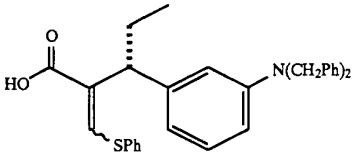

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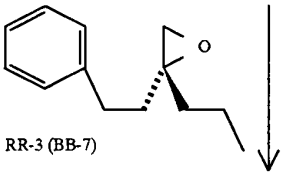

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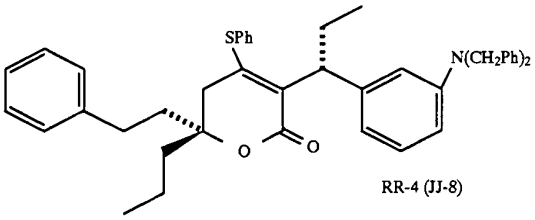
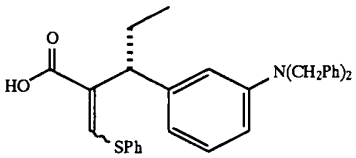


RR-4 (JJ-8)

CHART SS



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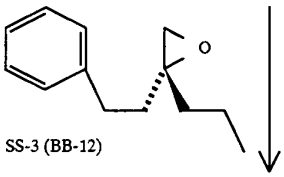

SS-3 (BB-12)

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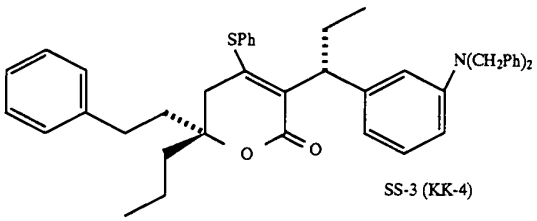
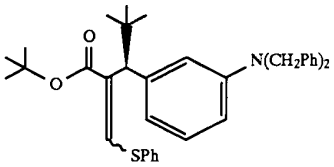
CHART SS



SS-3 (KK-4)

CHART TT



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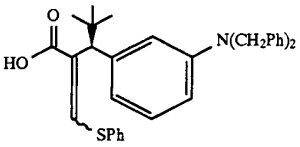

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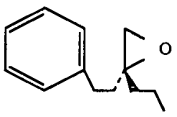

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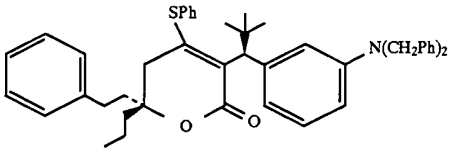
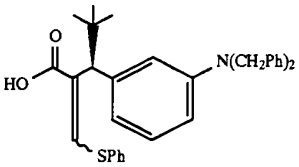


TT-4 (LL-8)

CHART UU



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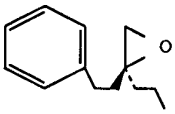

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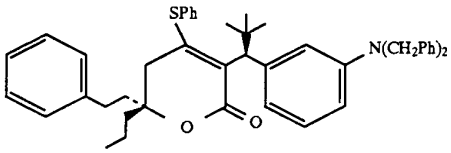

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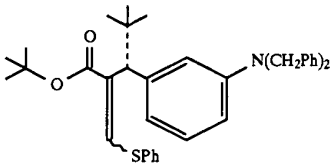

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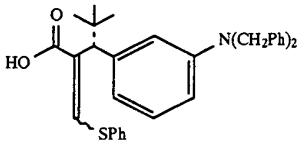

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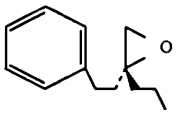

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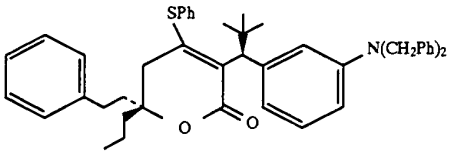

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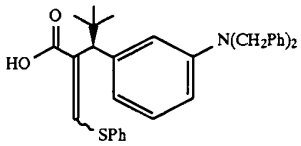

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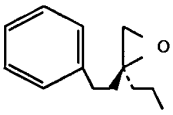

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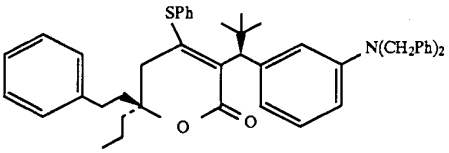

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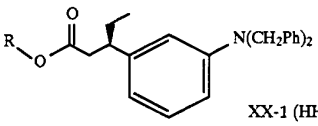

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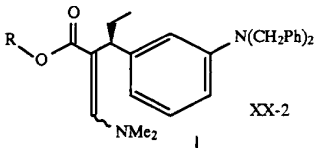

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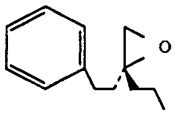

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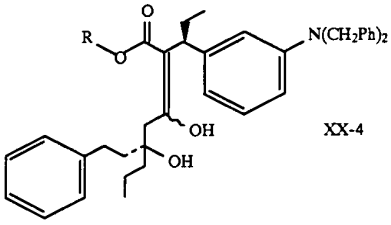

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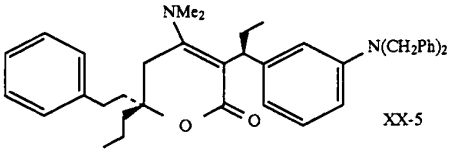

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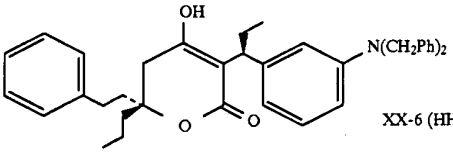

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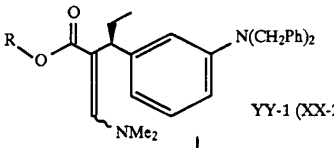

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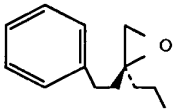

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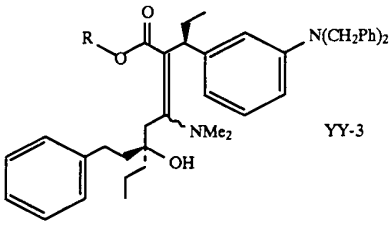

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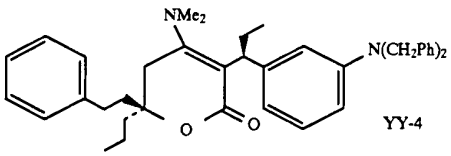

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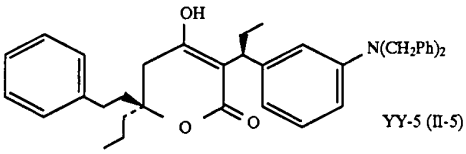

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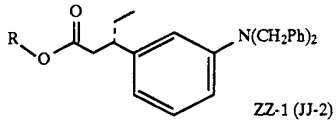

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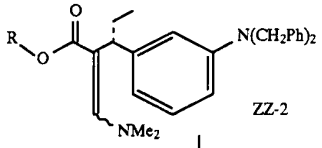

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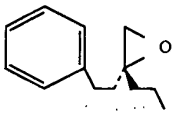

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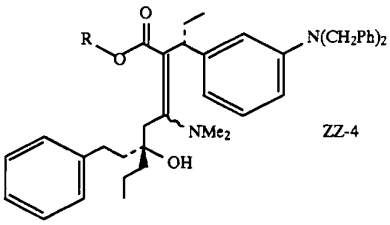

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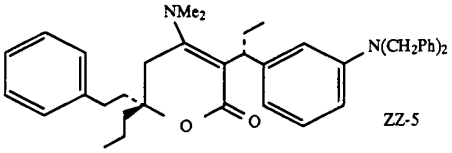

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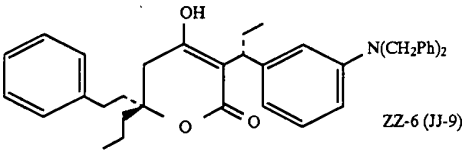

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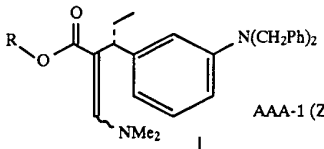

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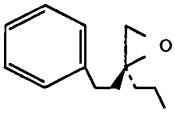

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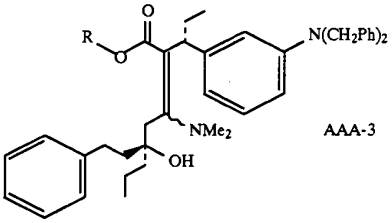

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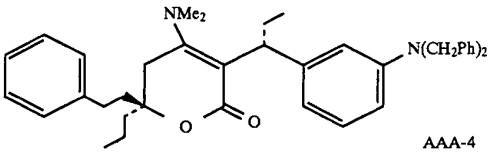

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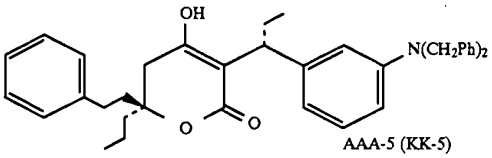

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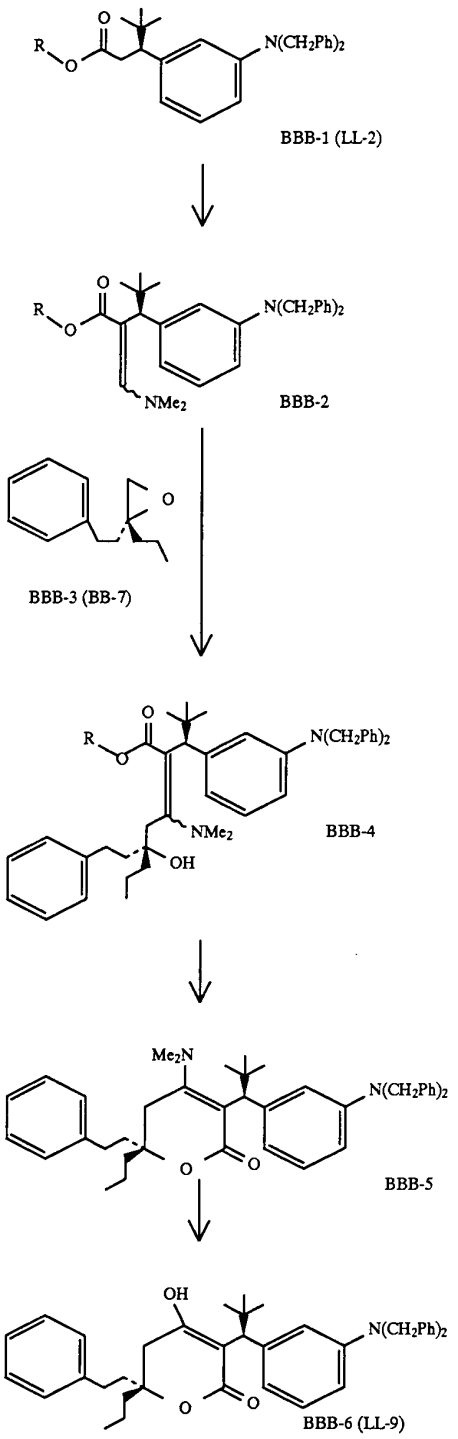

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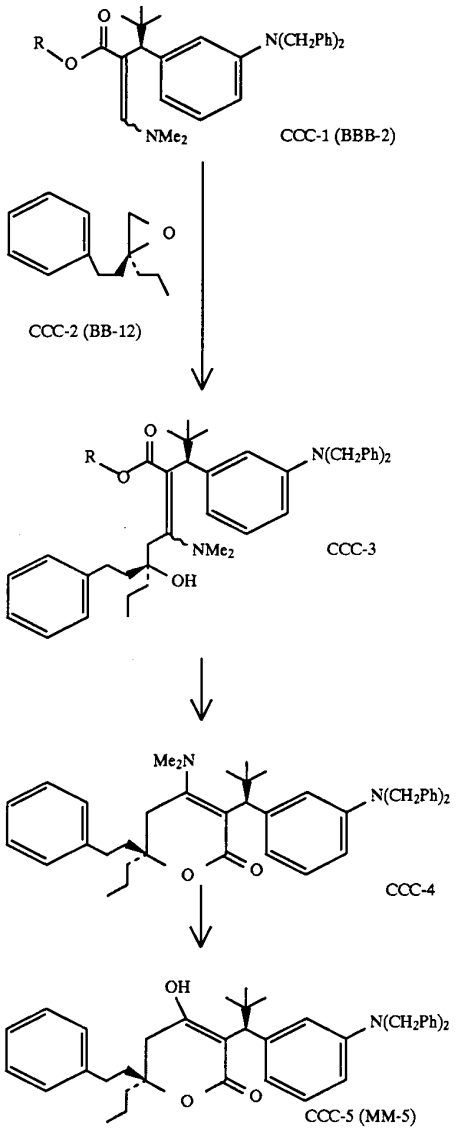

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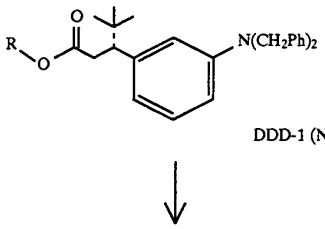

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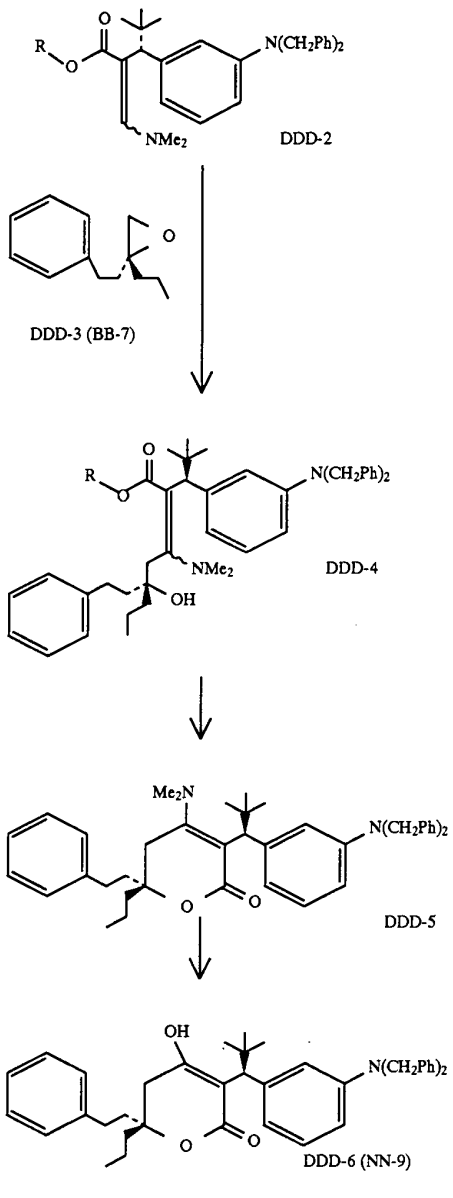

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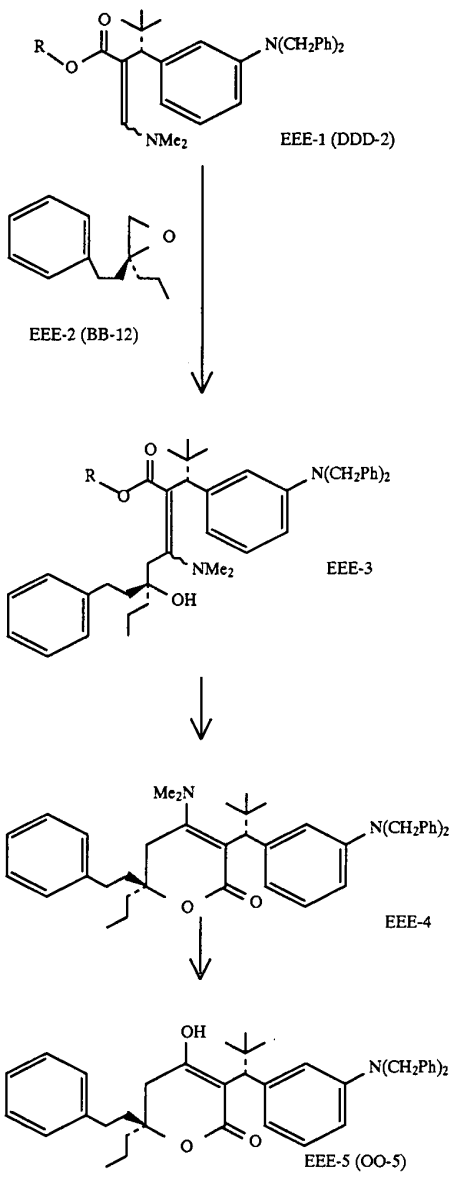

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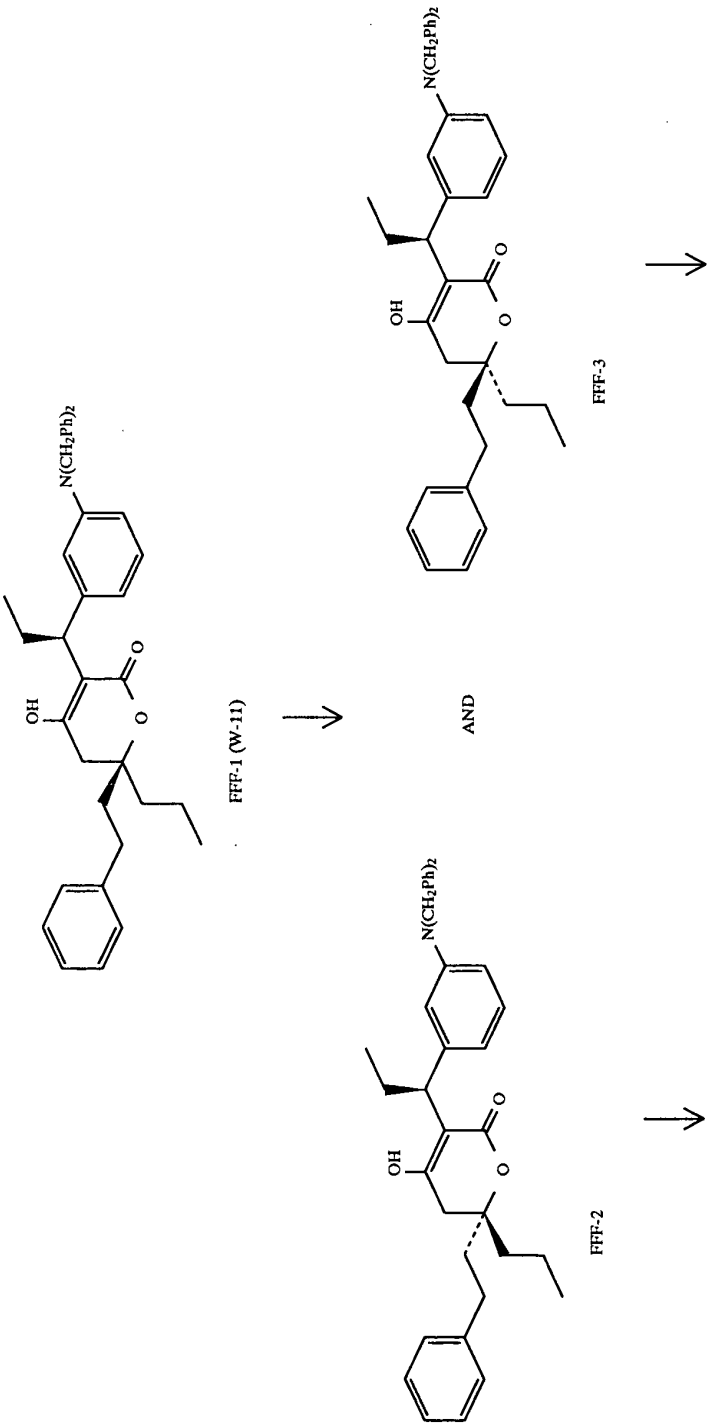

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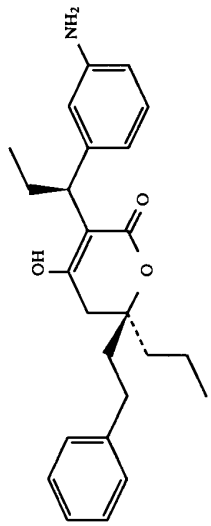

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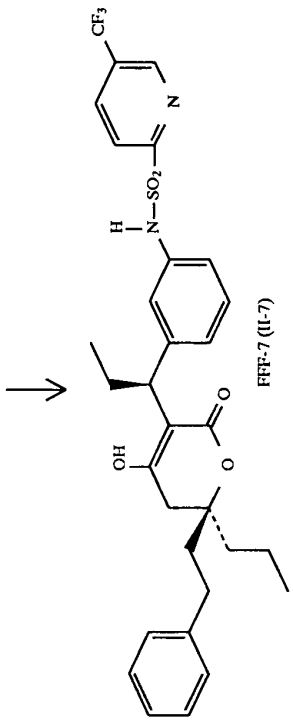

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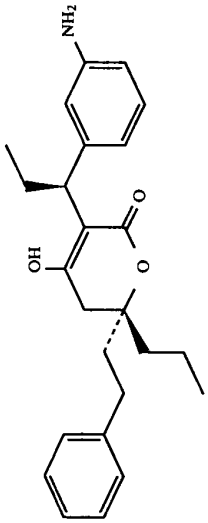

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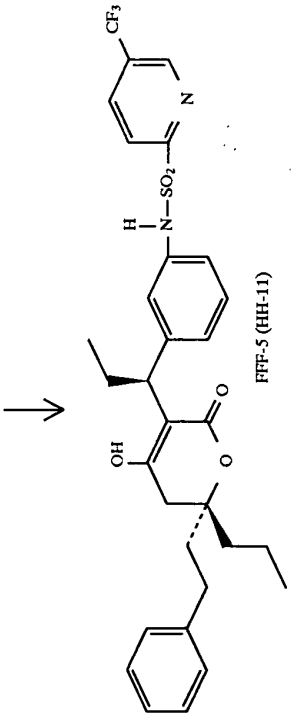

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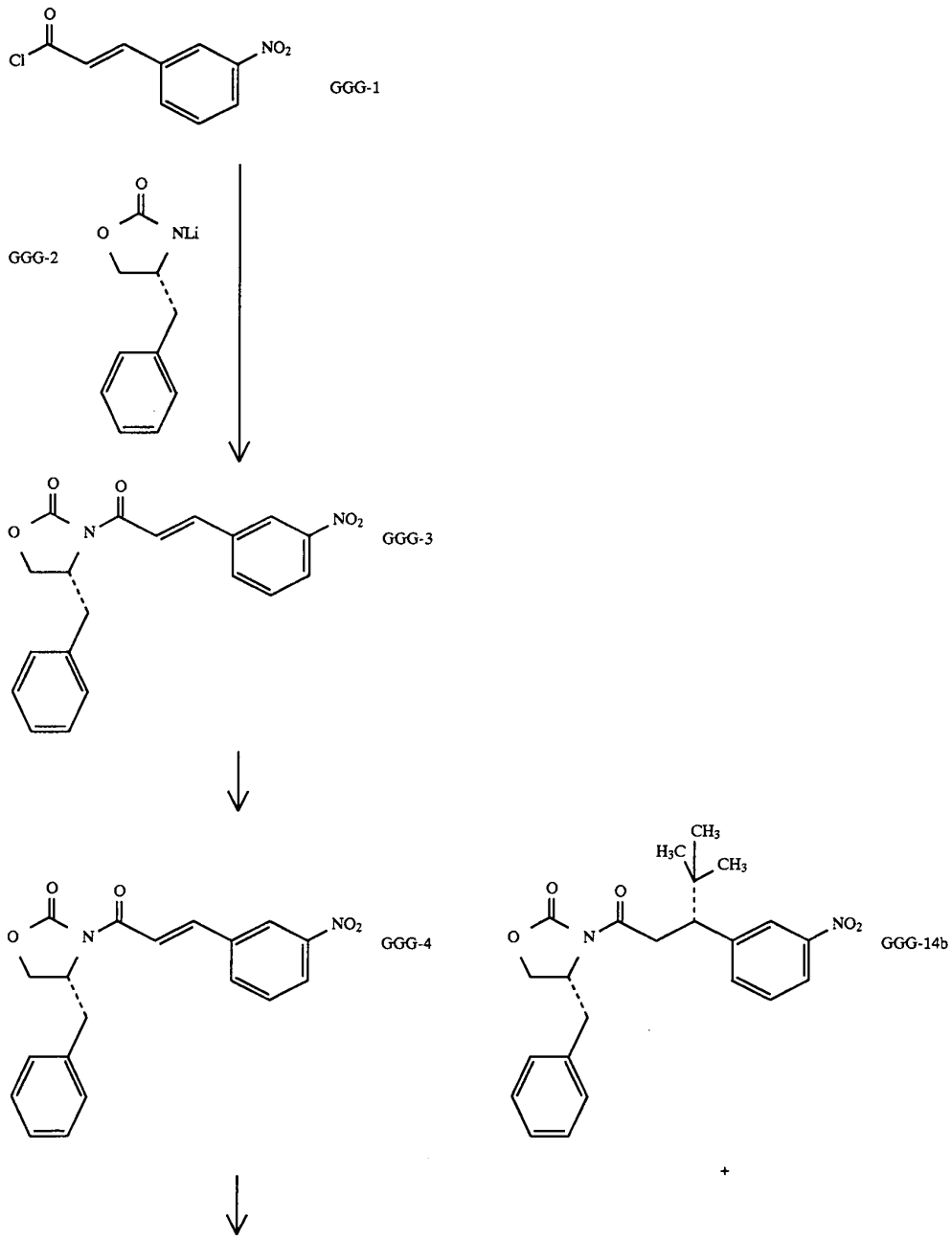

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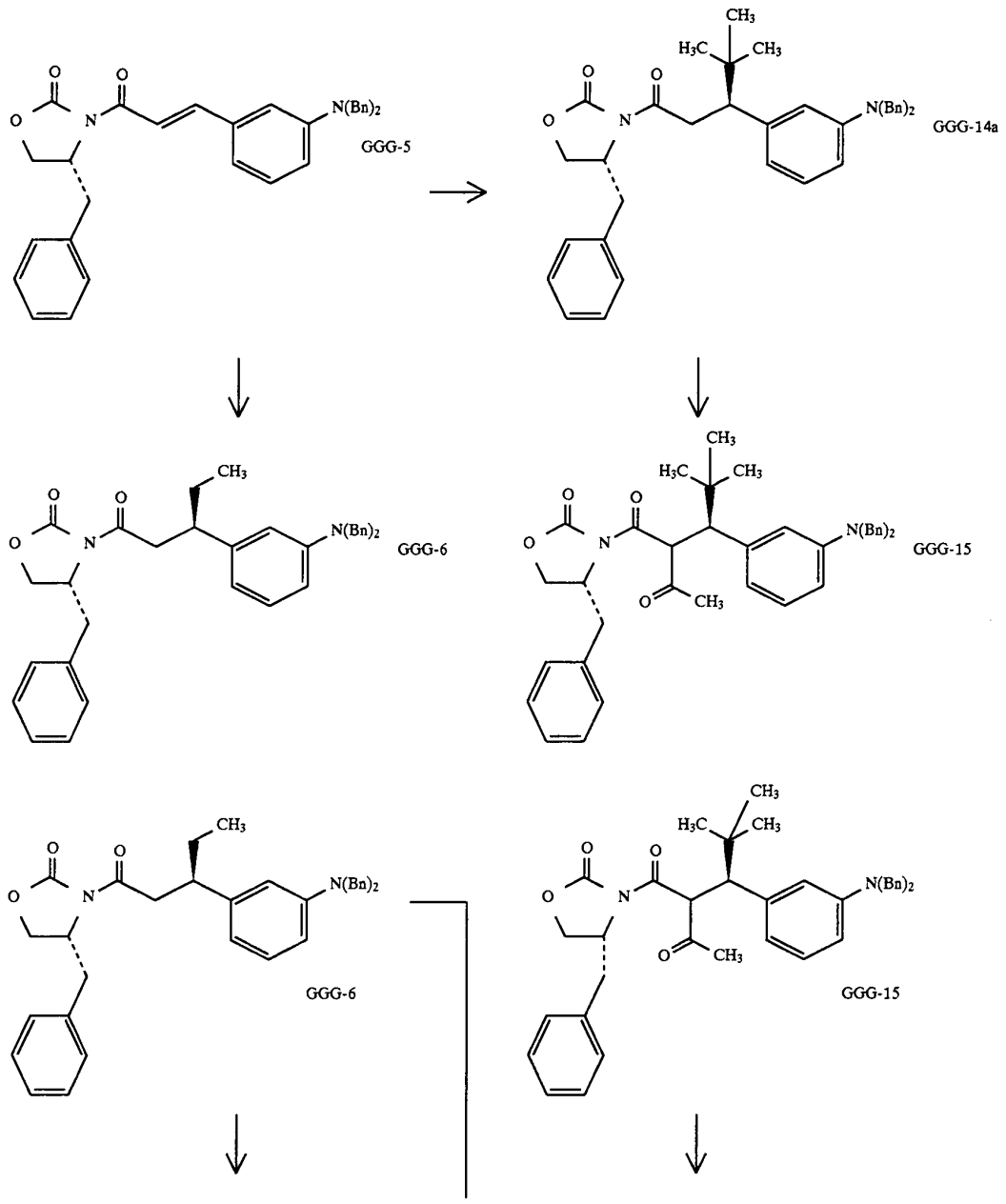

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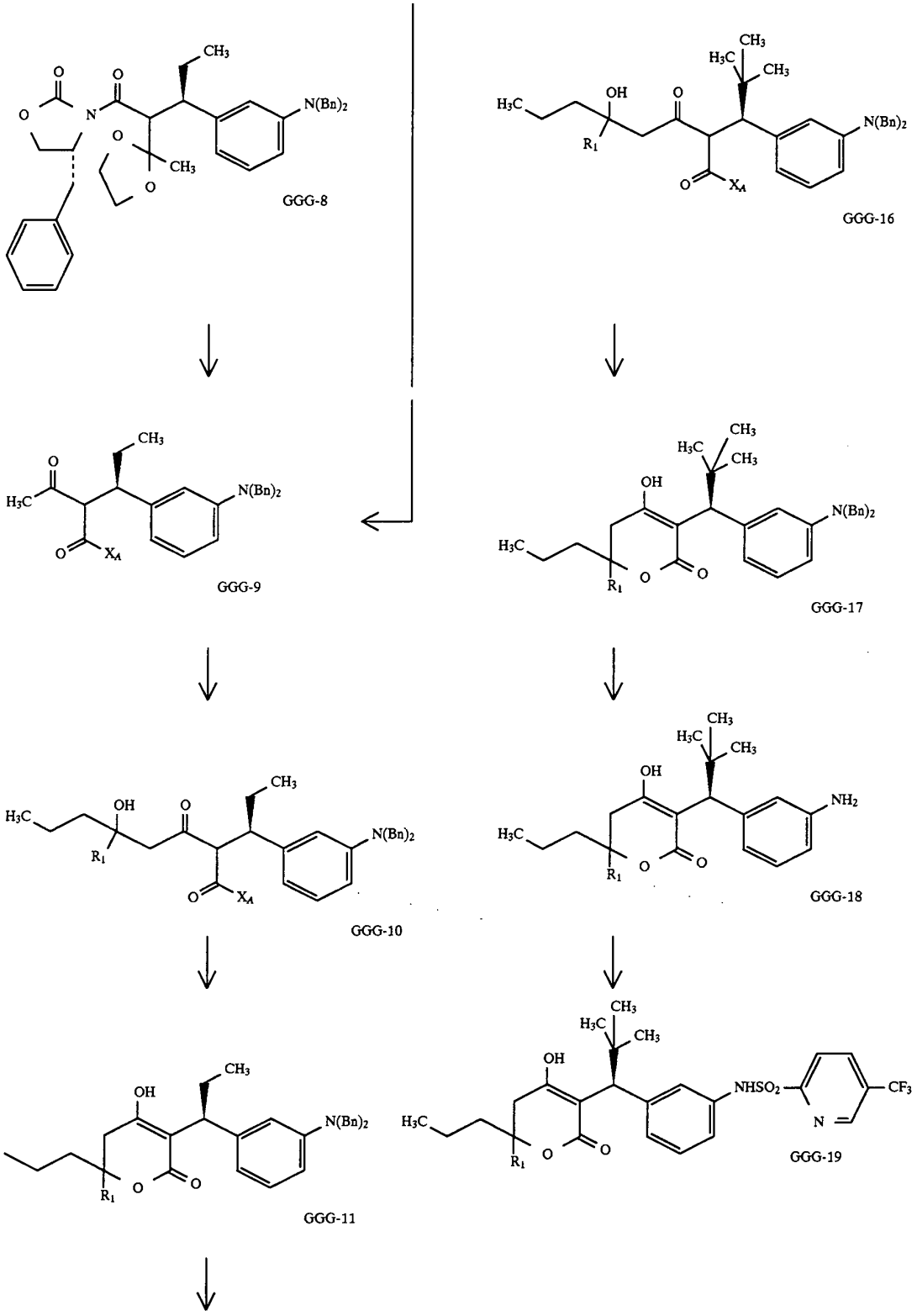

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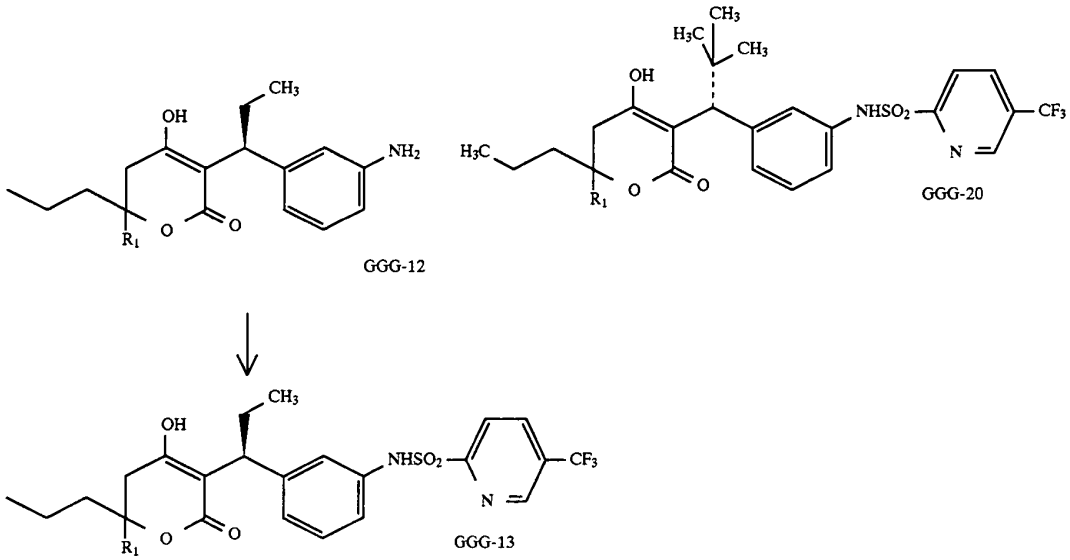

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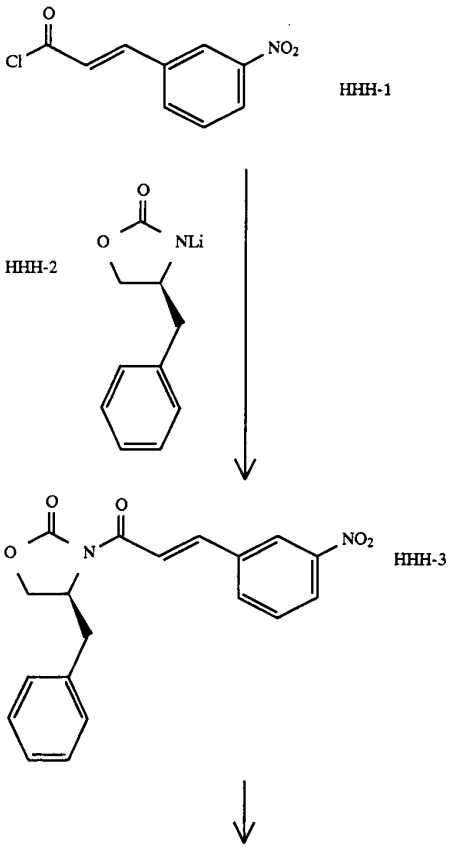

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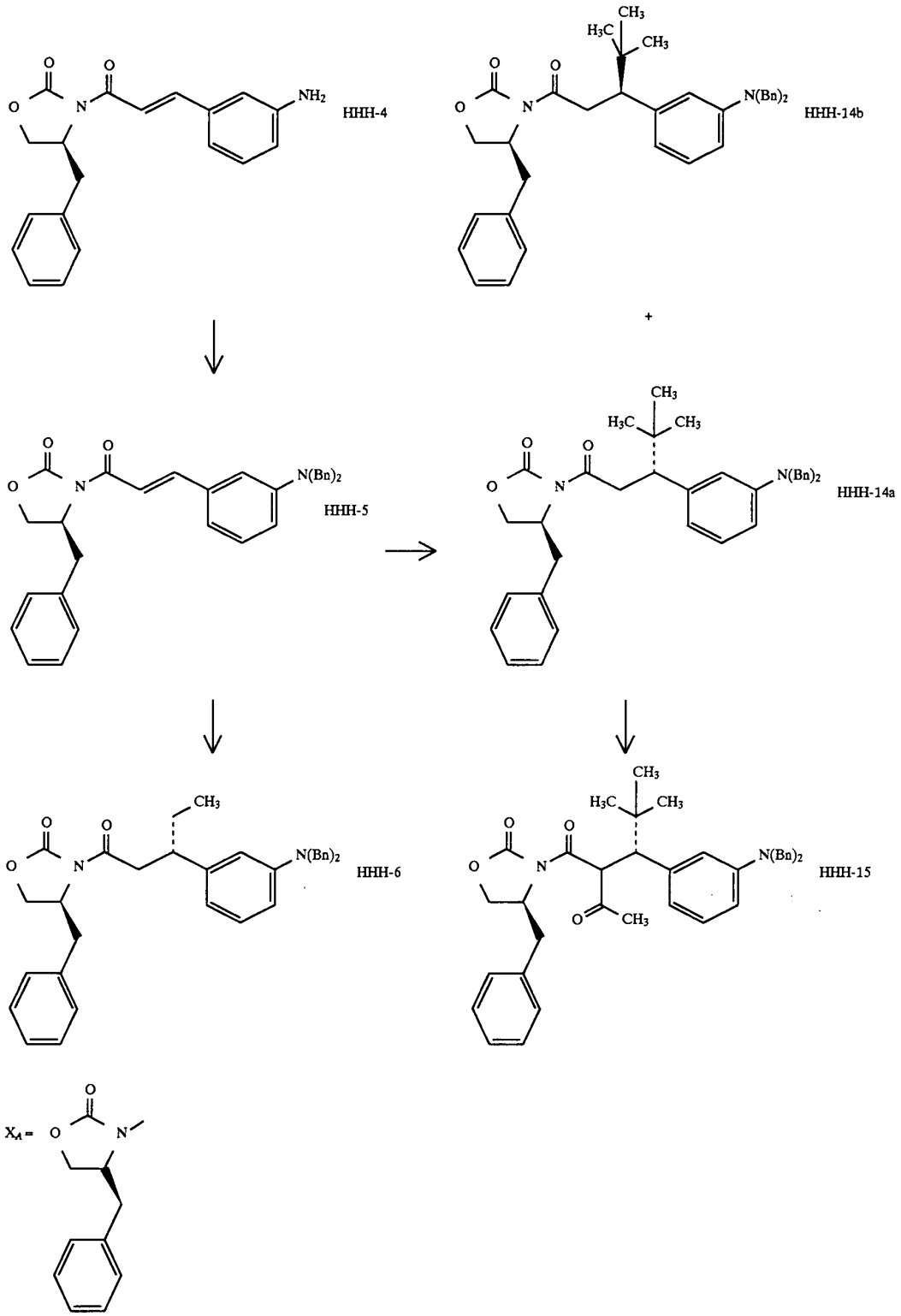

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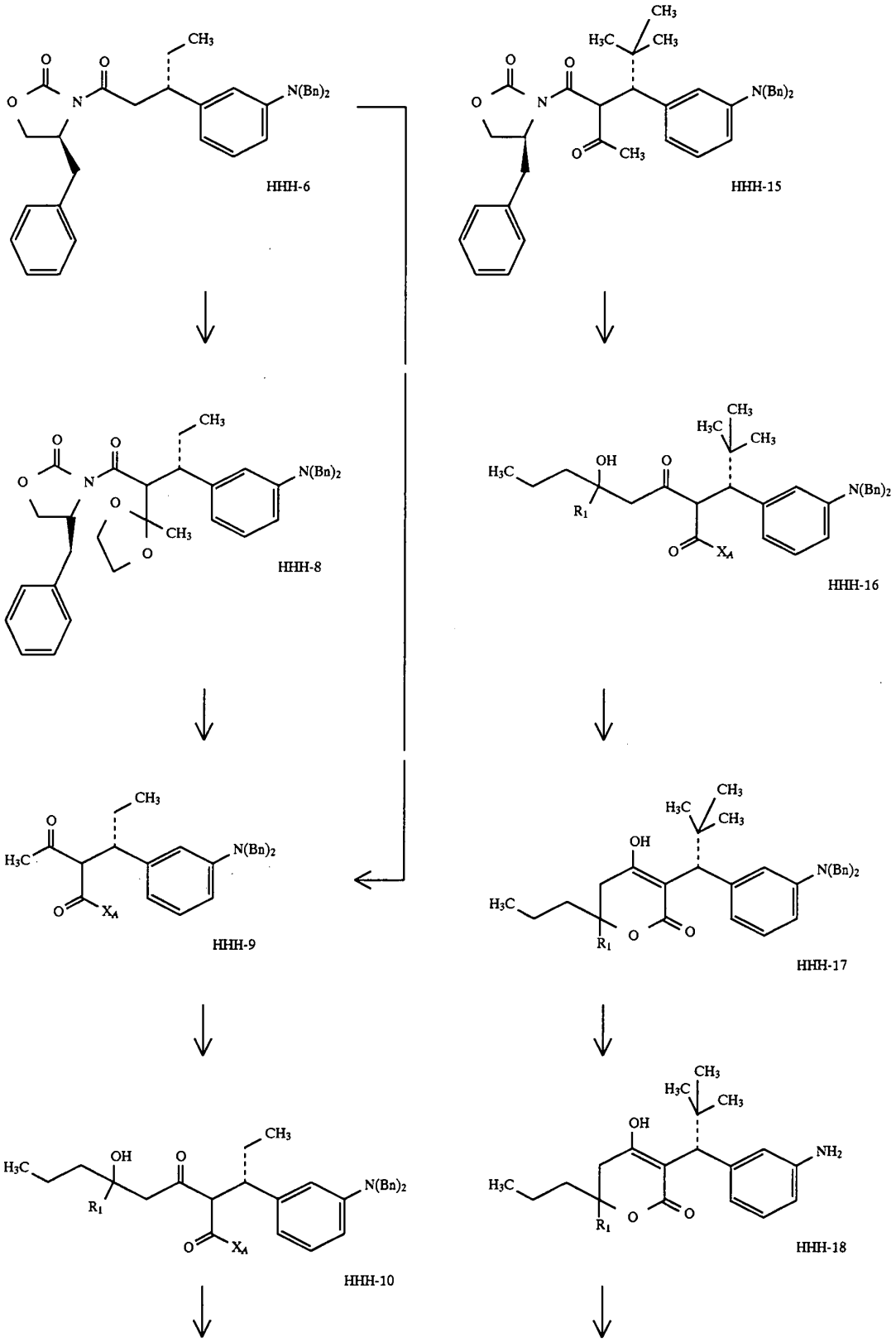

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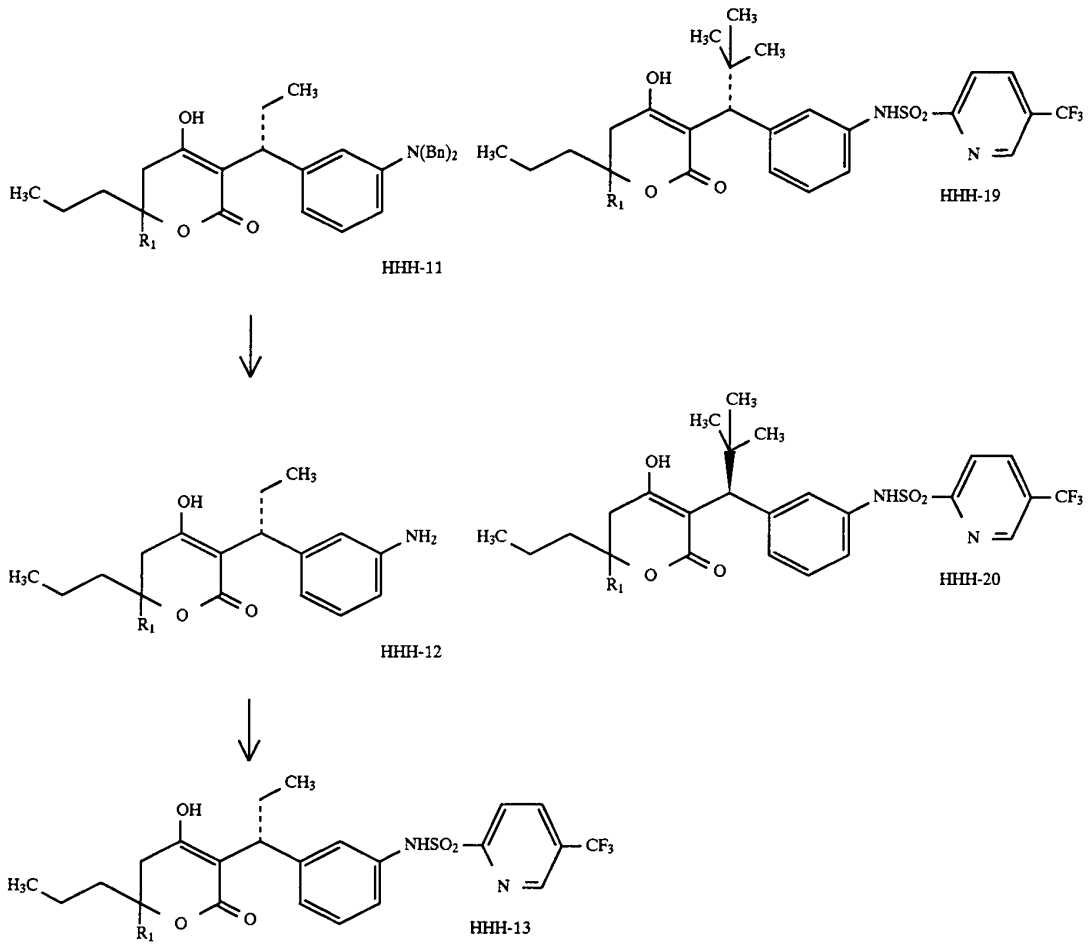

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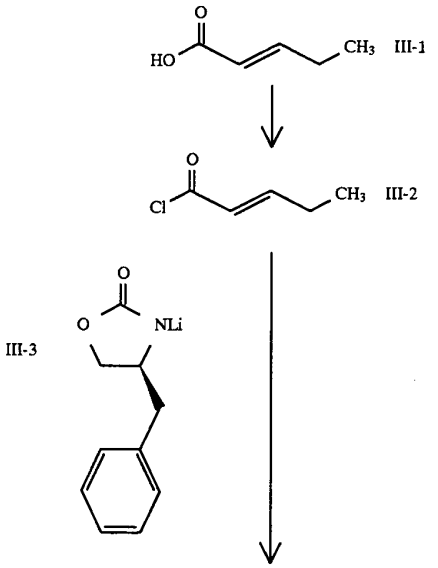

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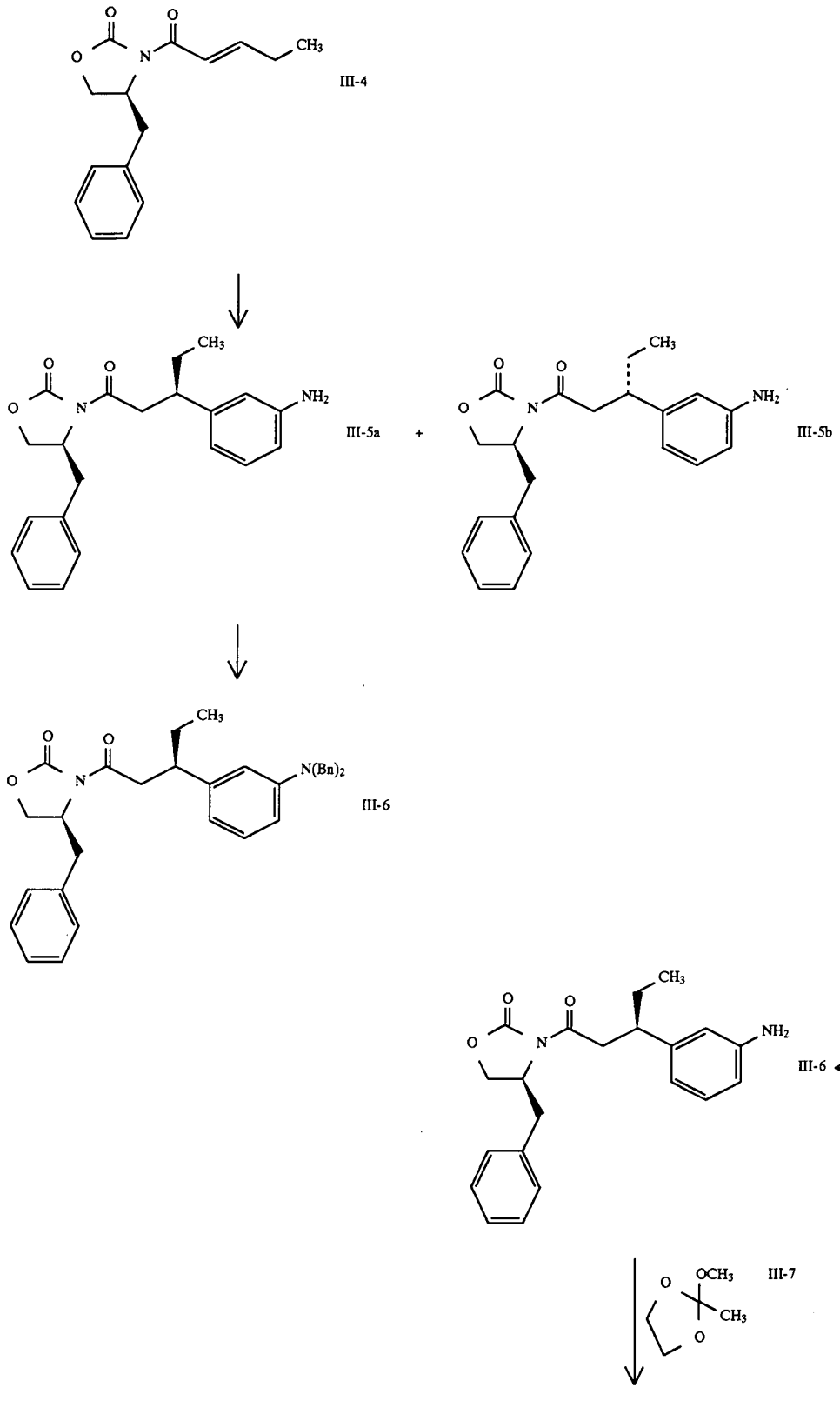

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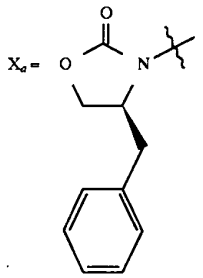

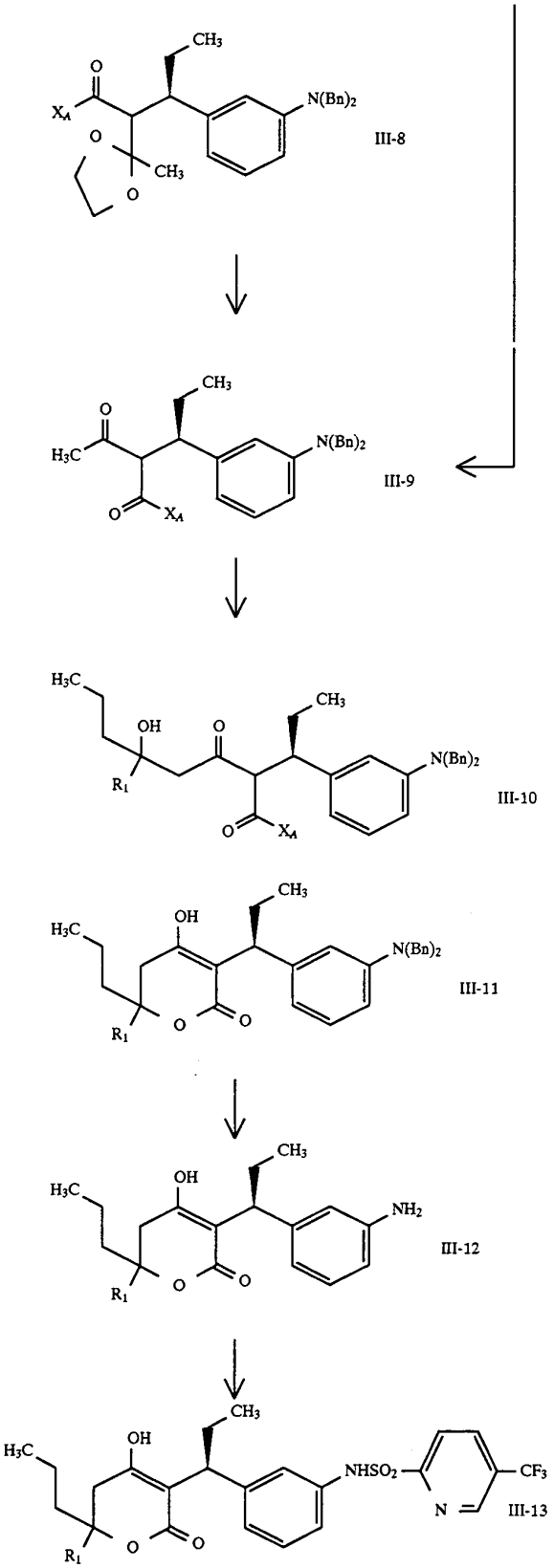

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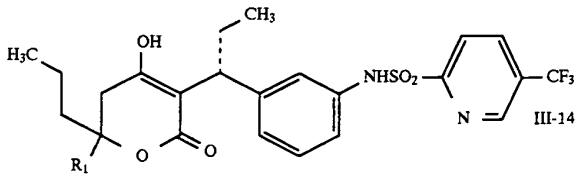

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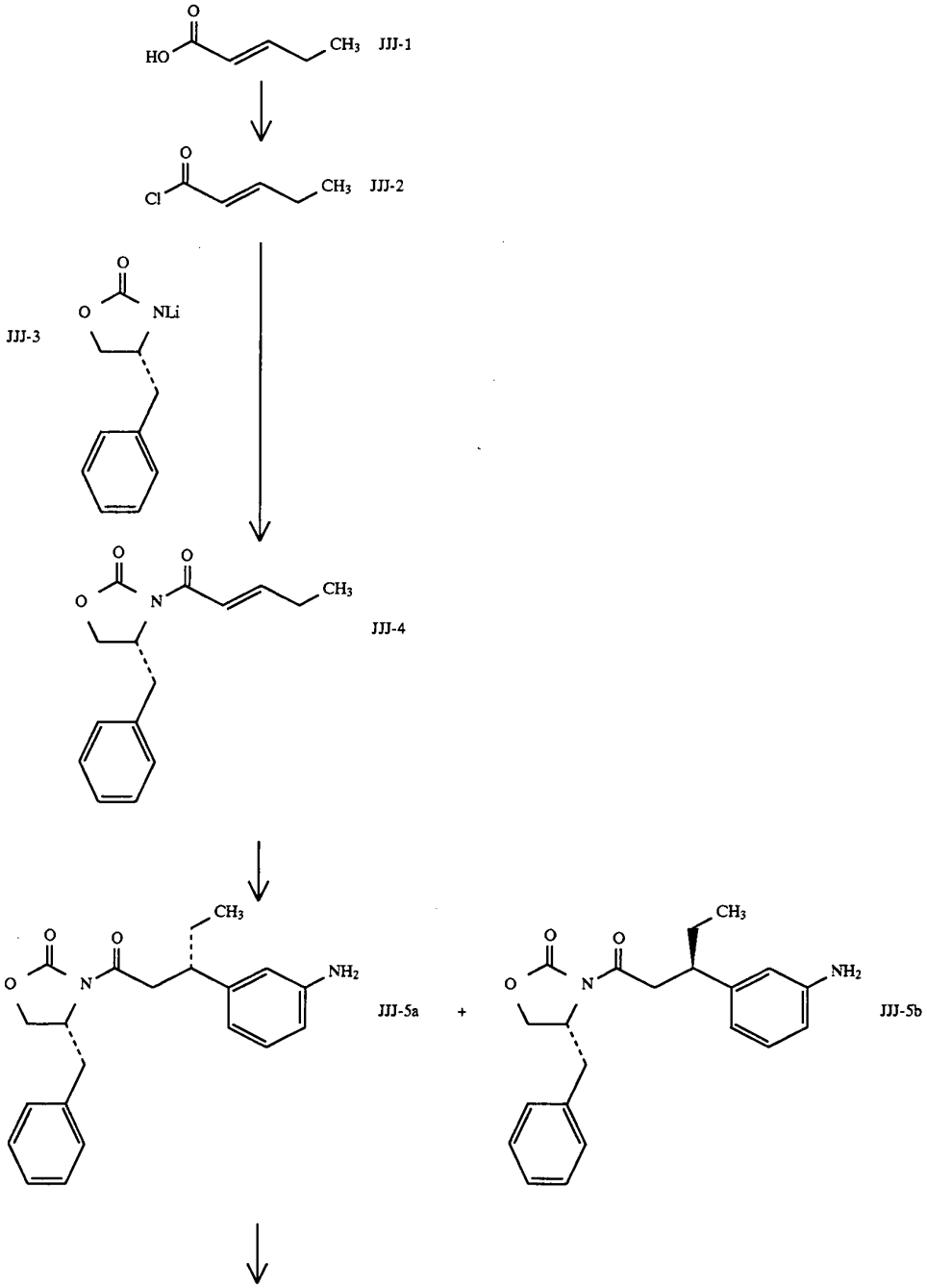

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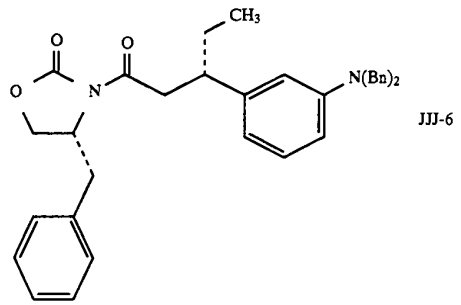

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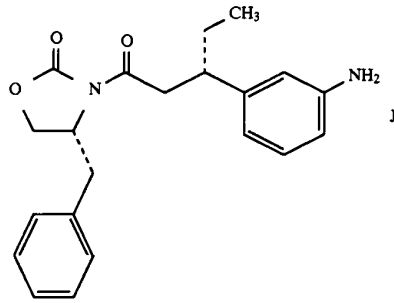

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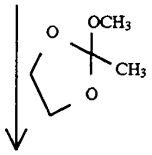

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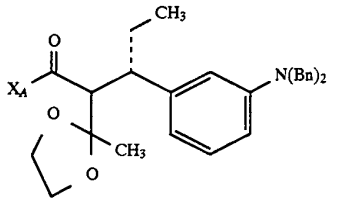
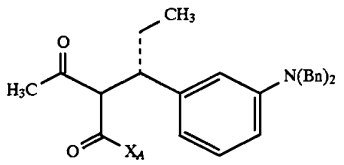


JJJ-8



JJJ-9

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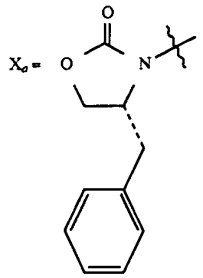
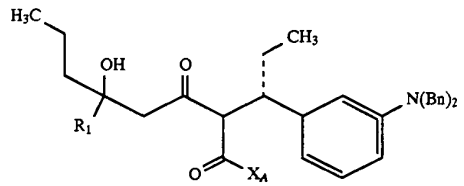
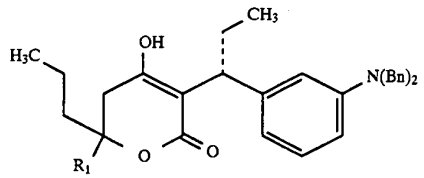
CHART JJJ





JJJ-10



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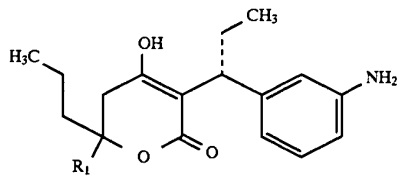
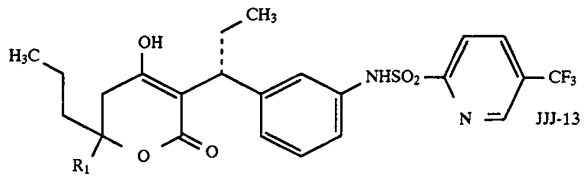
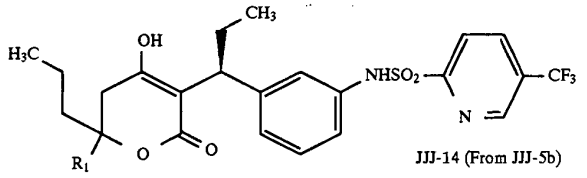


JJJ-12

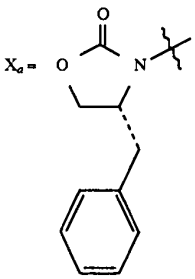


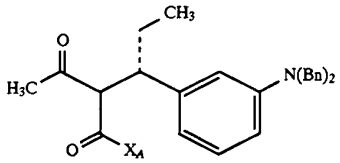
JJJ-13



JJJ-14 (From JJJ-5b)

CHART KKK





KKK-1 (JJJ-9)

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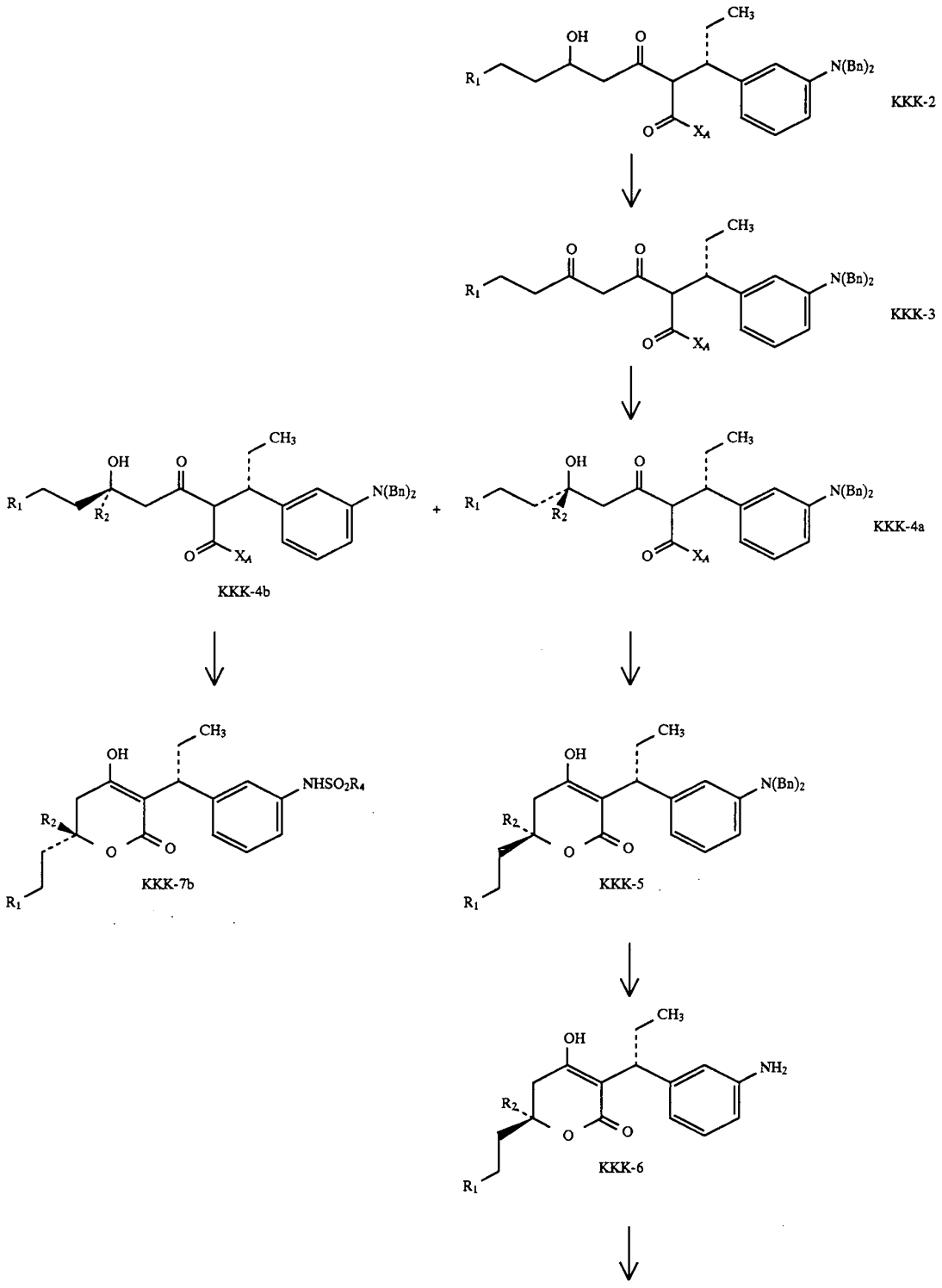

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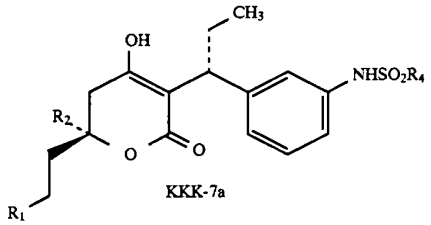
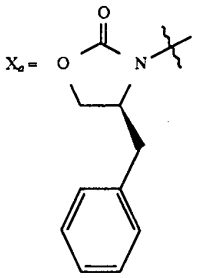
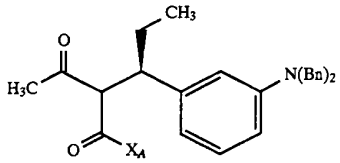
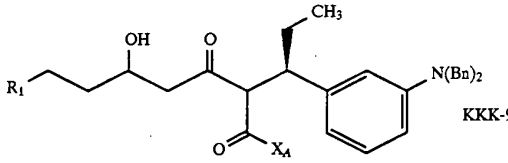


KKK-7a

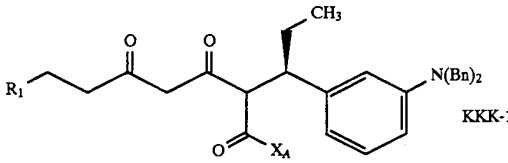




KKK-8 (III-6)



KKK-9



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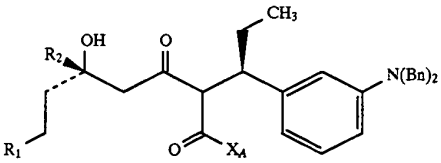

KKK-11b

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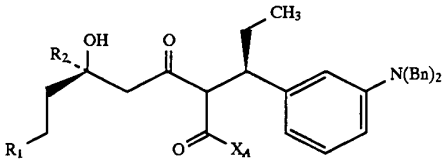

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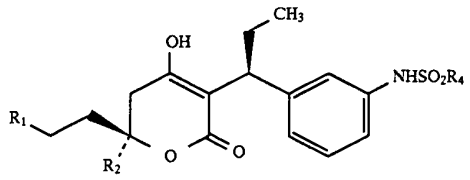

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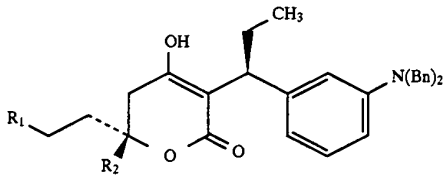

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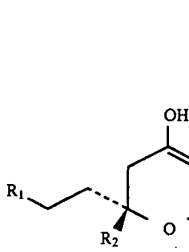

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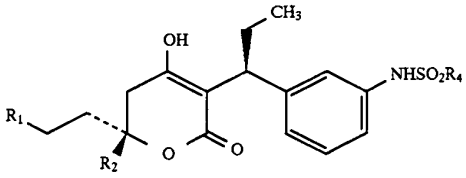
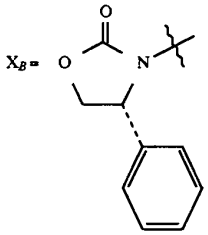
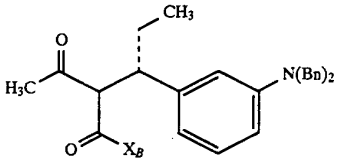
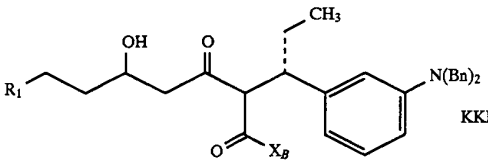


KKK-14a





KKK-15(X-6)



KKK-16

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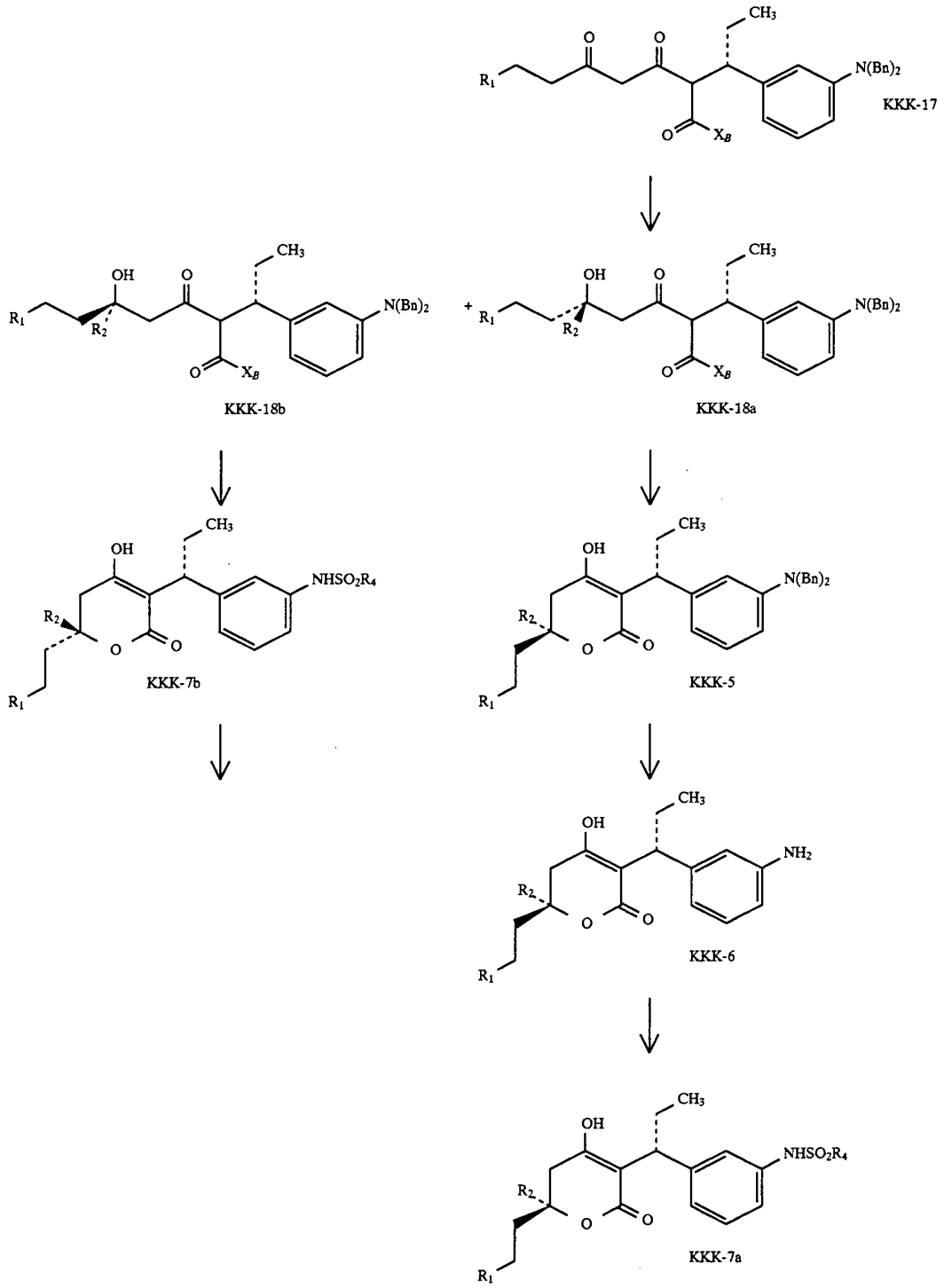
CHART KKK



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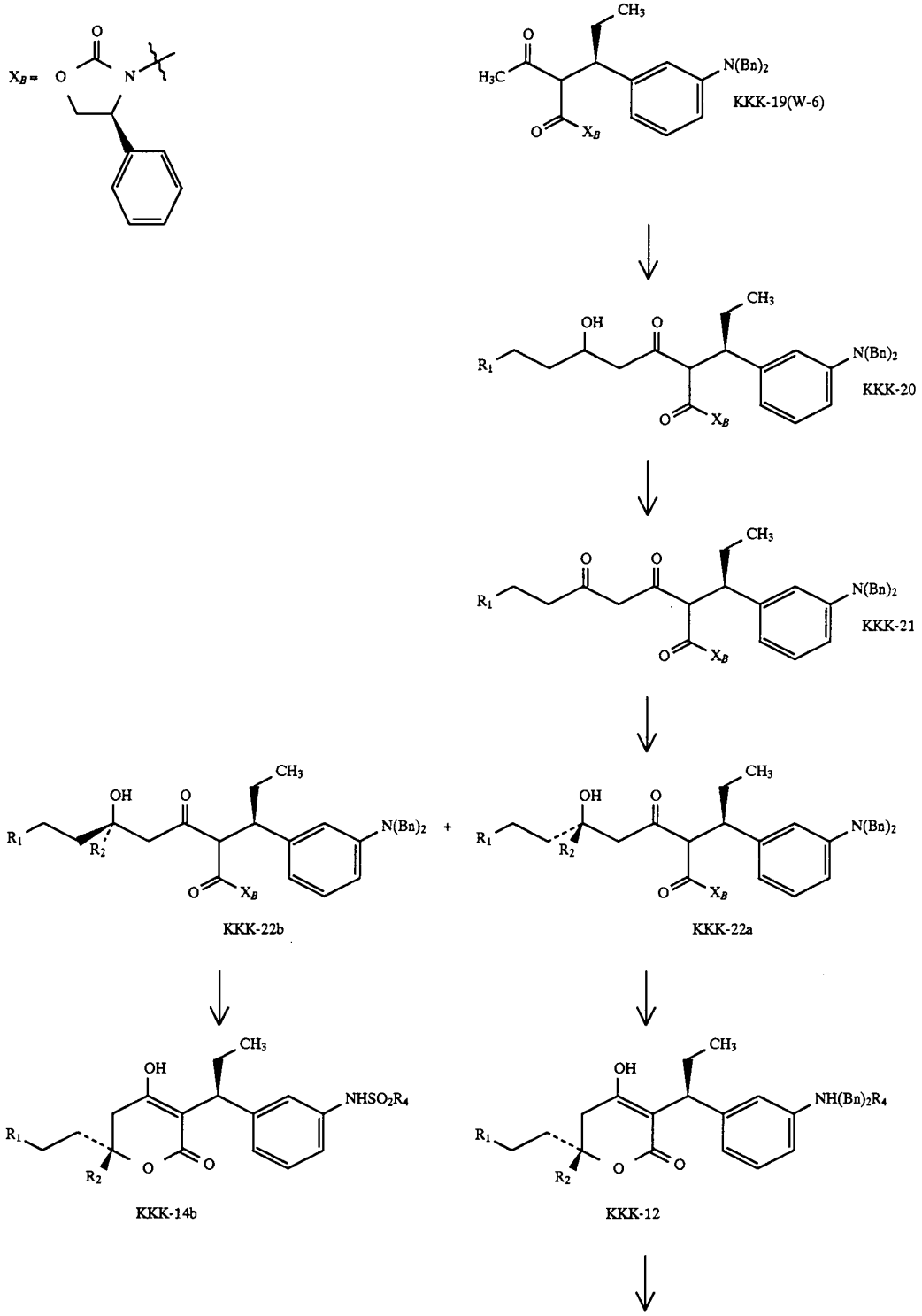

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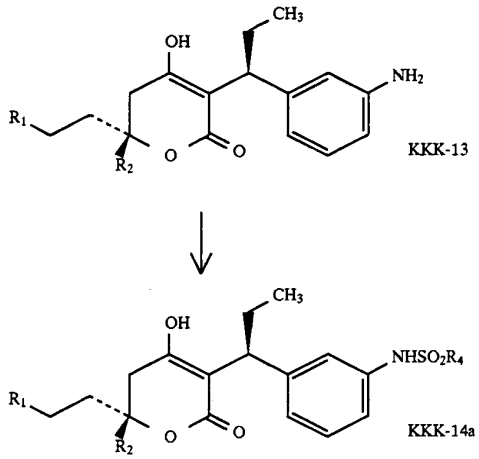

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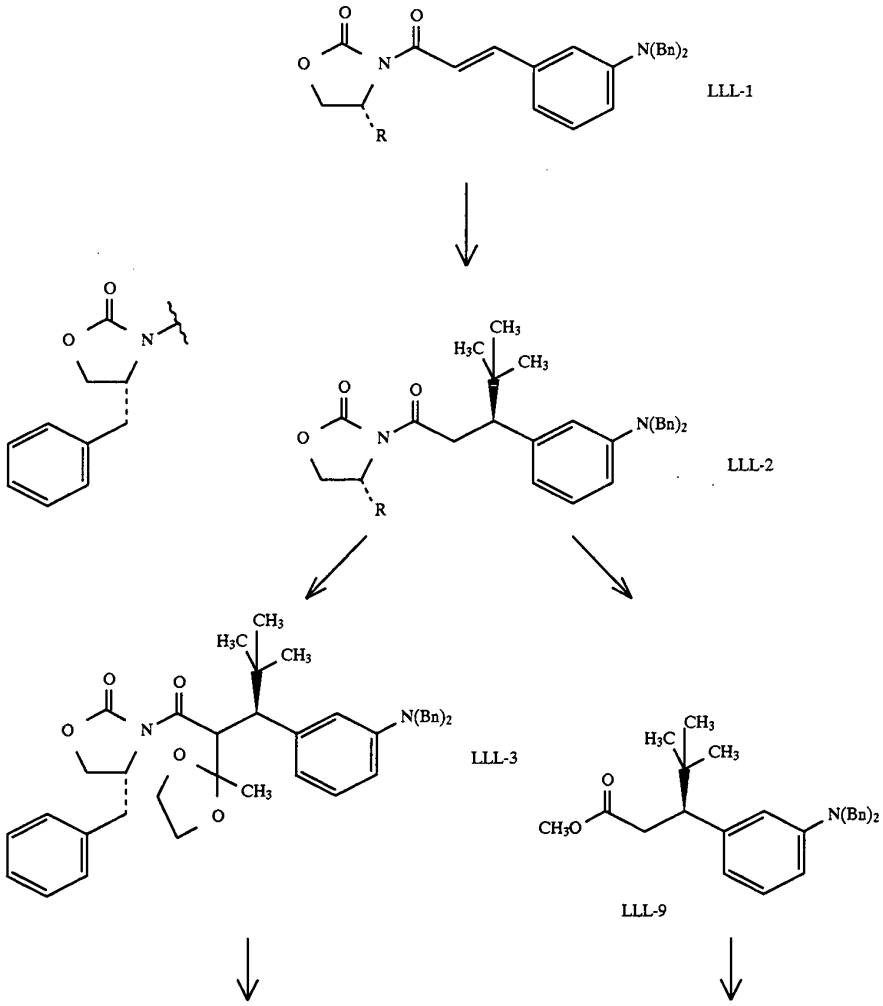

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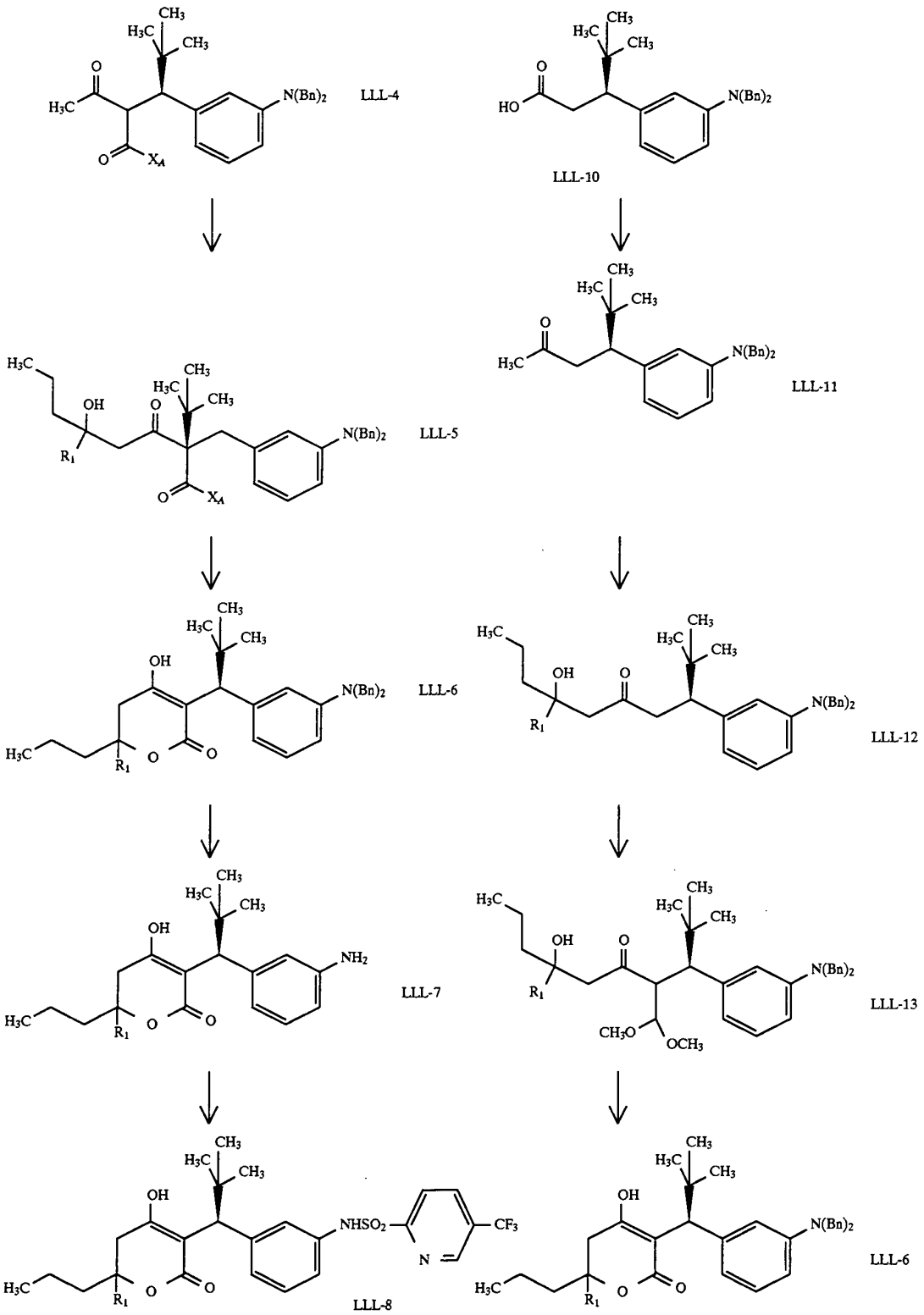

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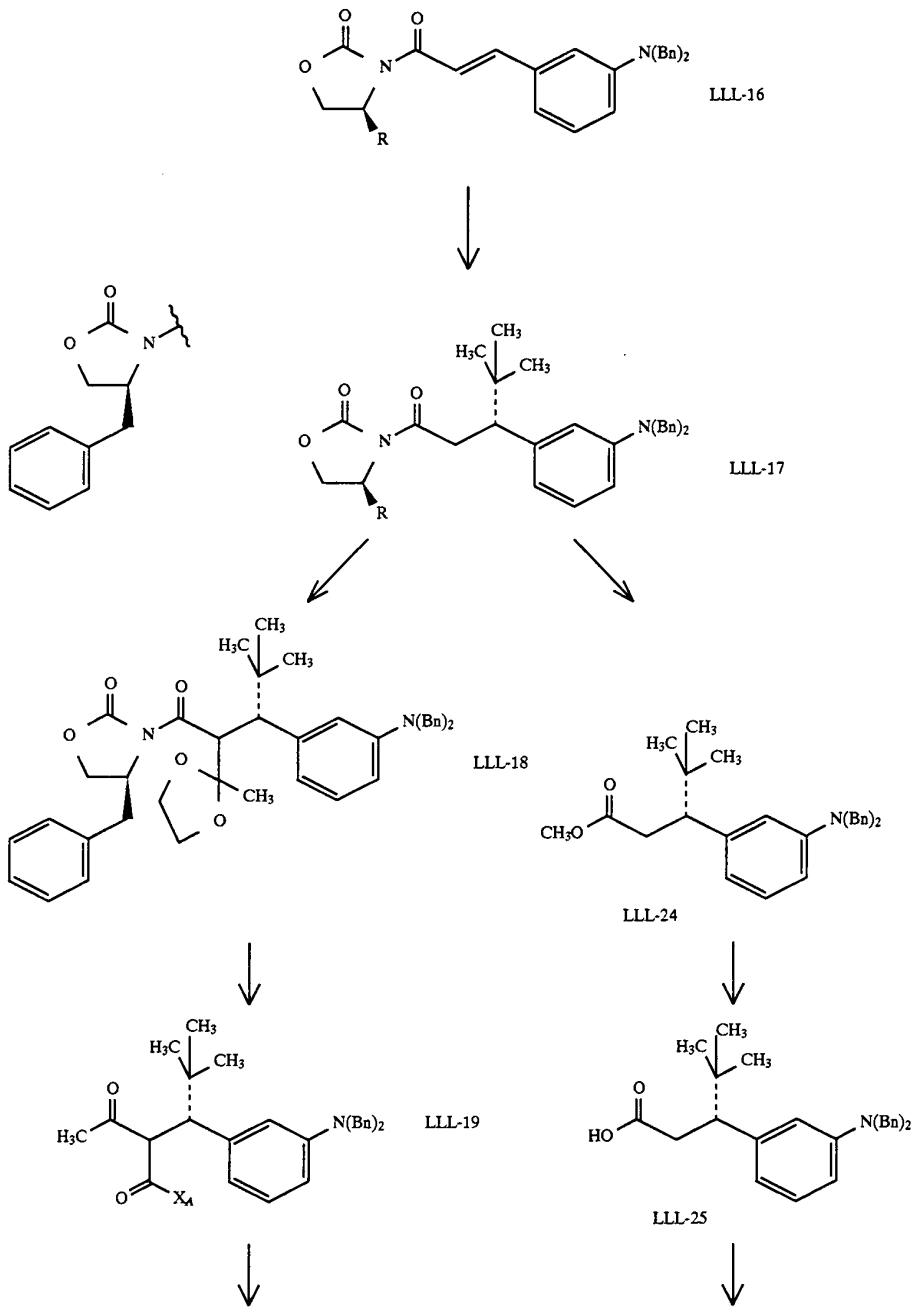

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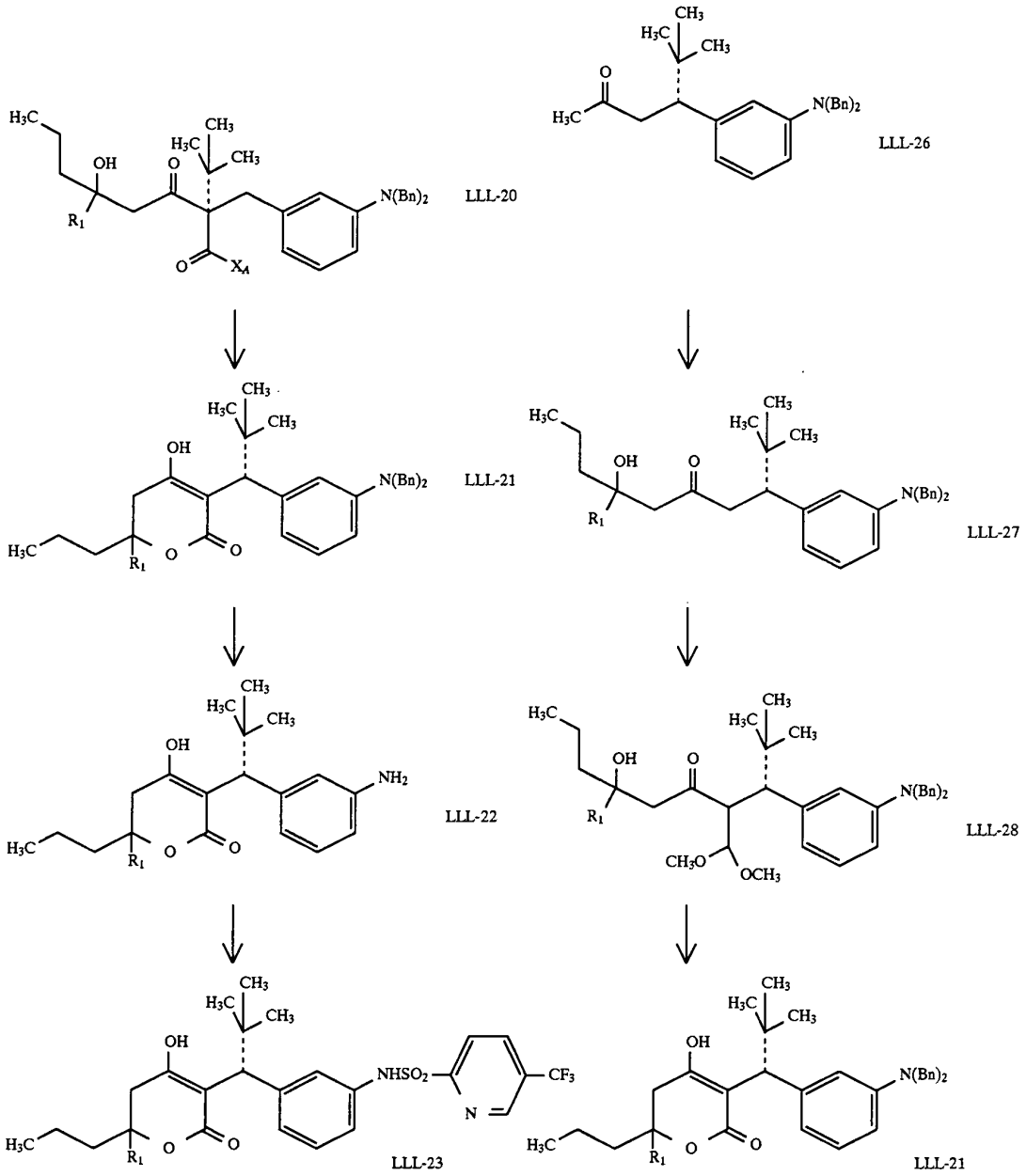
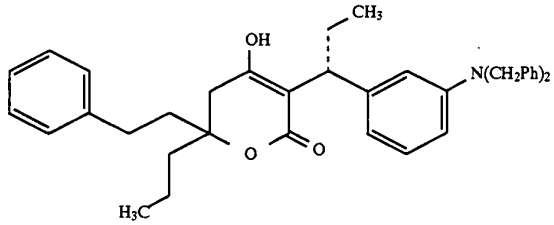
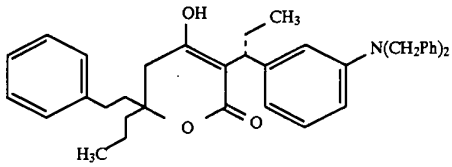


CHART MMM



MMM-1 (X-11)



MMM-2

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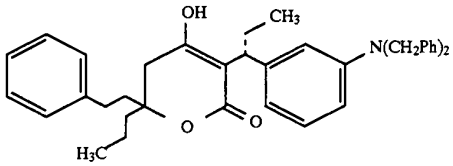

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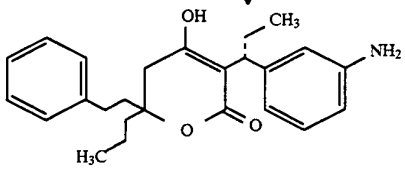
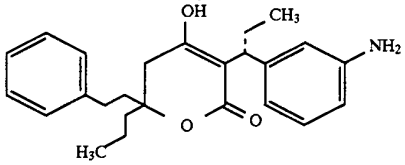


MMM-4



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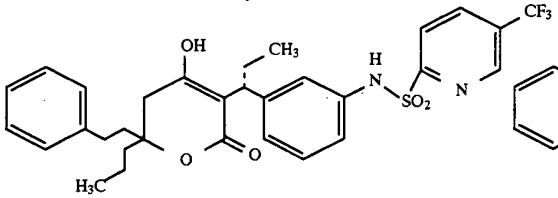
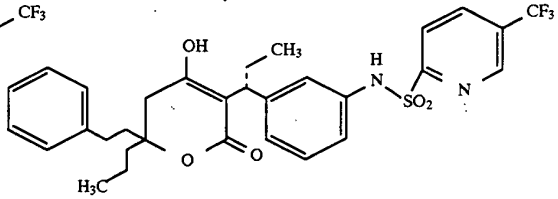
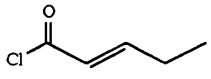


MMM-5

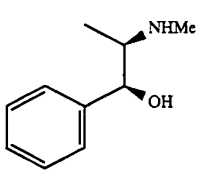


MMM-7

CHART NNN



NNN-1 (W-2)



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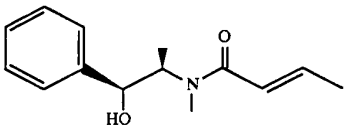

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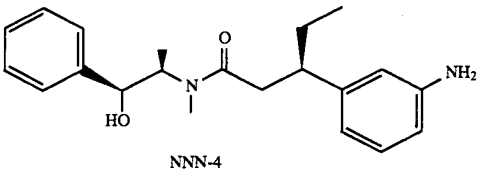

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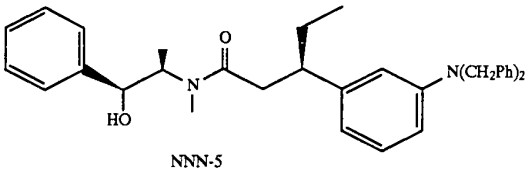

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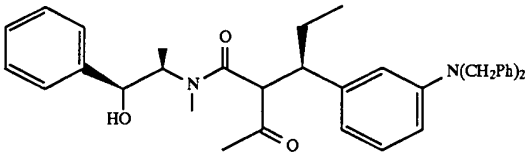

NNN-6

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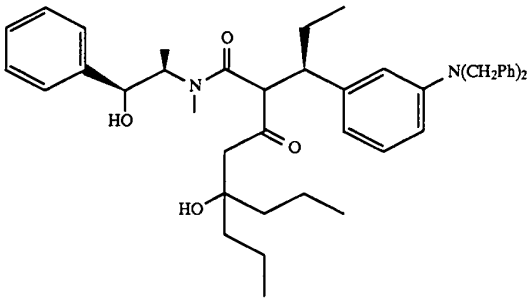
CHART NNN



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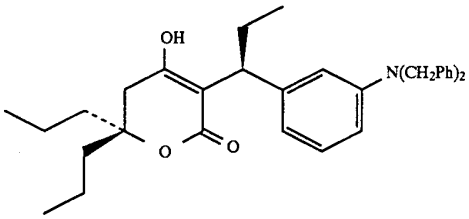
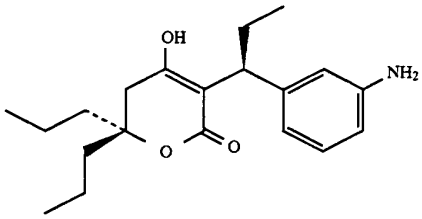
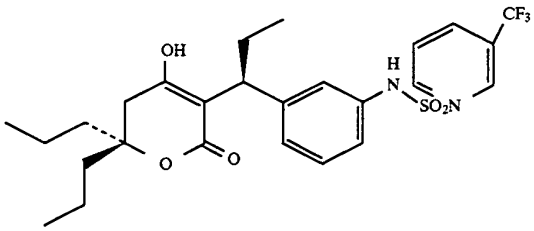


NNN-8

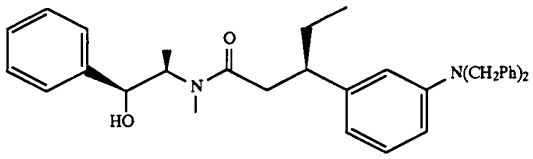


NNN-9

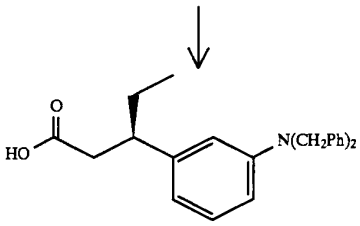


NNN-10 (W-13)

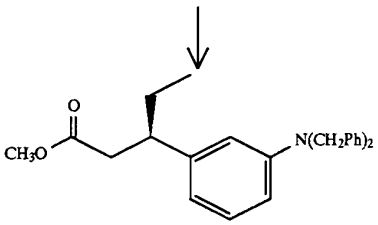
CHART OOO



OOO-1 (NNN-5)



OOO-2



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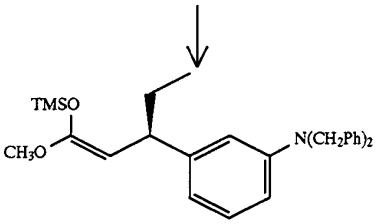
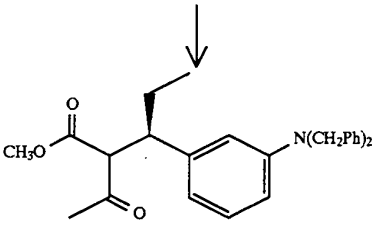
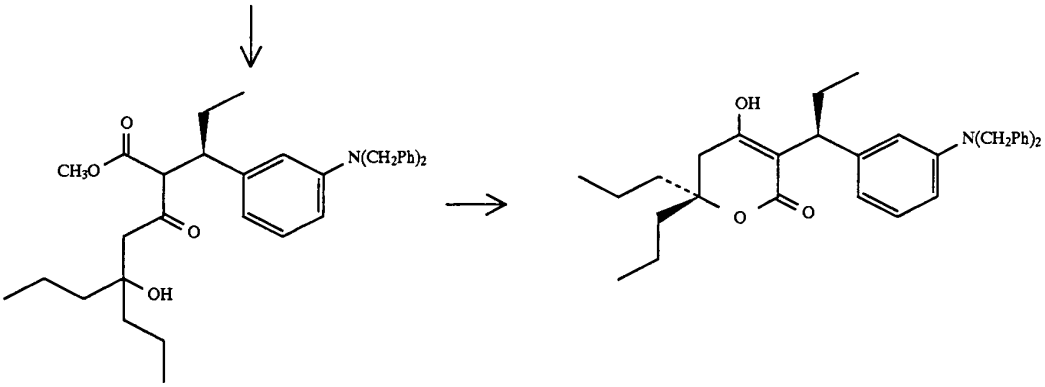


OOO-4



OOO-5



OOO-6 OOO-7 (NNN-8)

CHART PPP

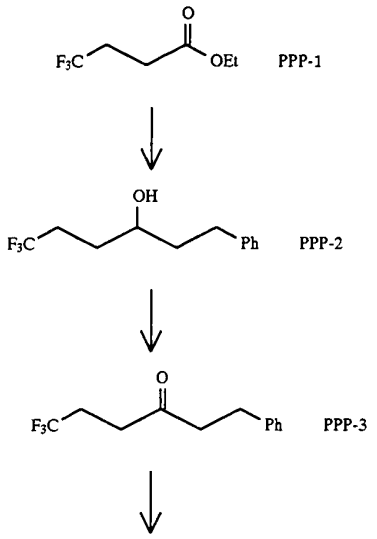


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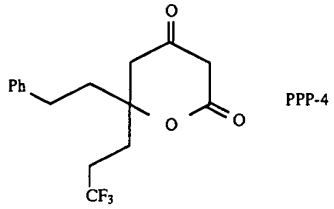
CHART PPP



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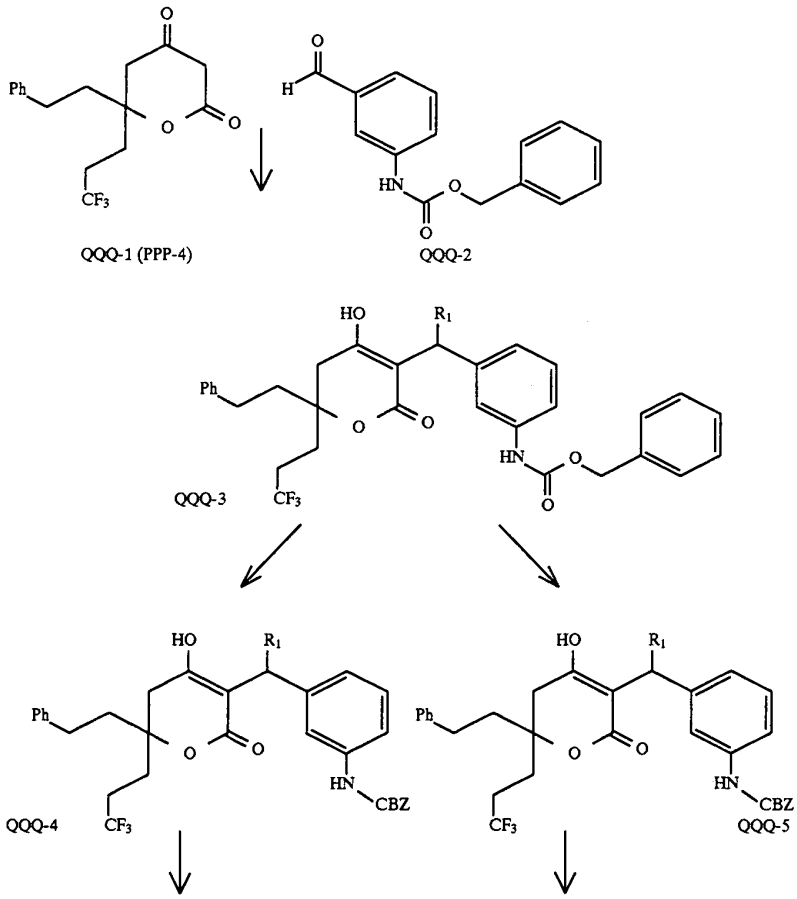

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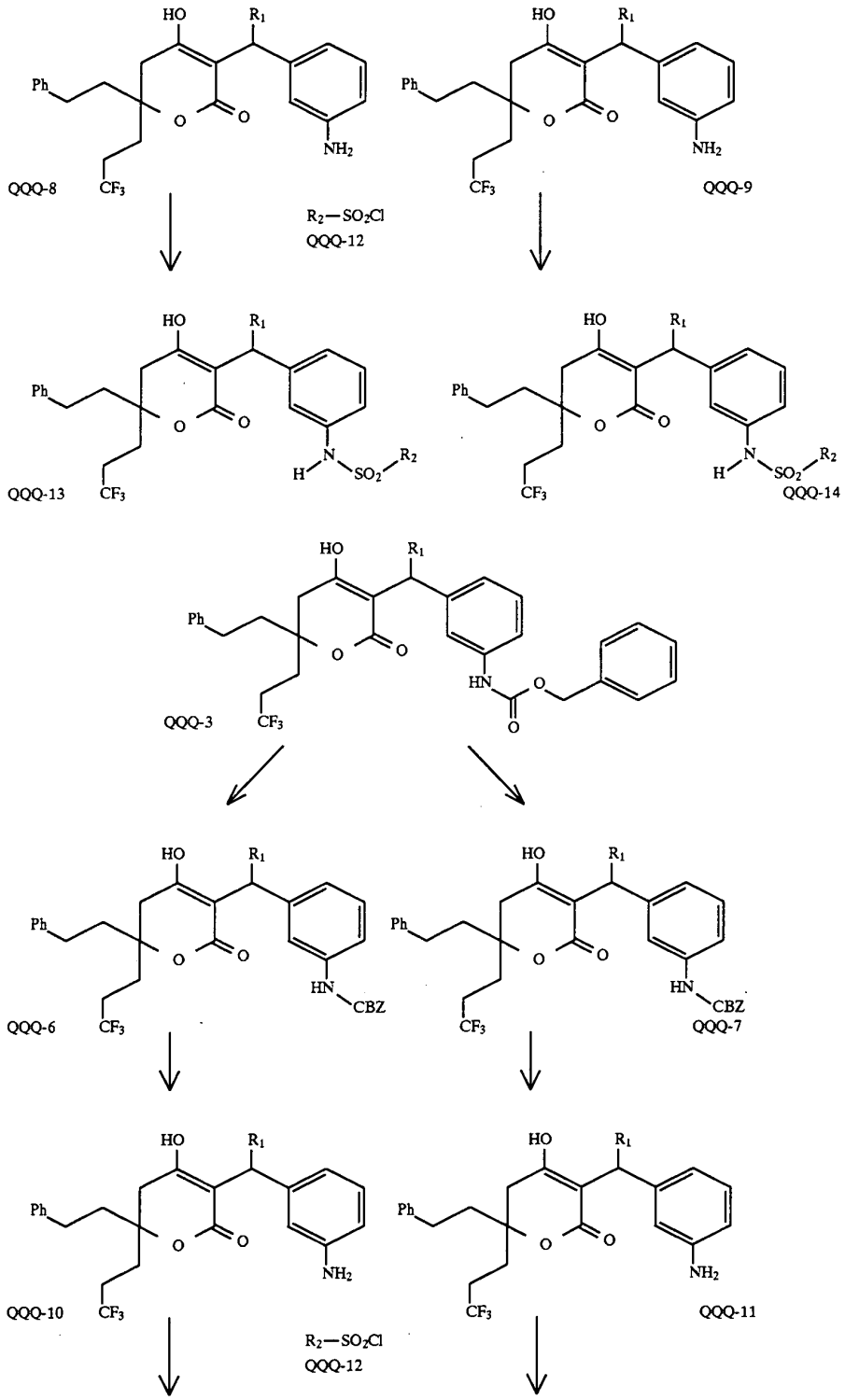

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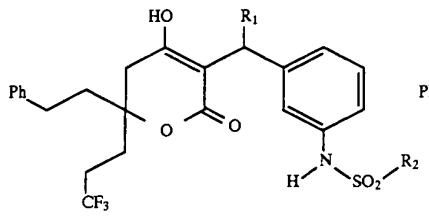
CHART QQQ



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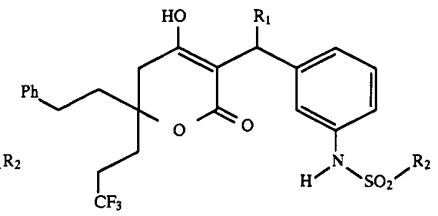

QQQ-16

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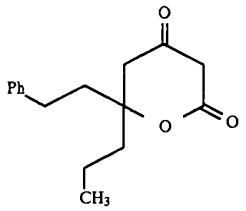

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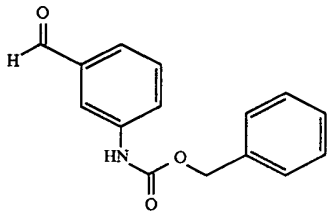

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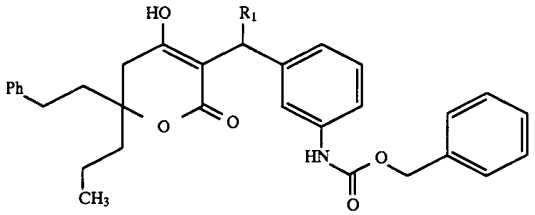

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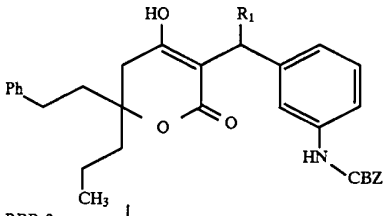

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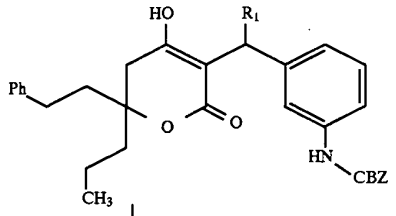

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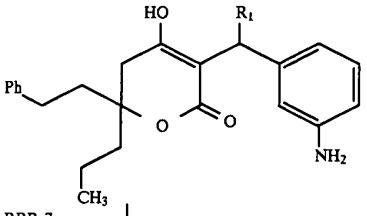

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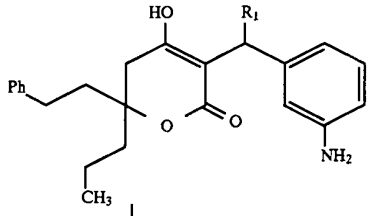

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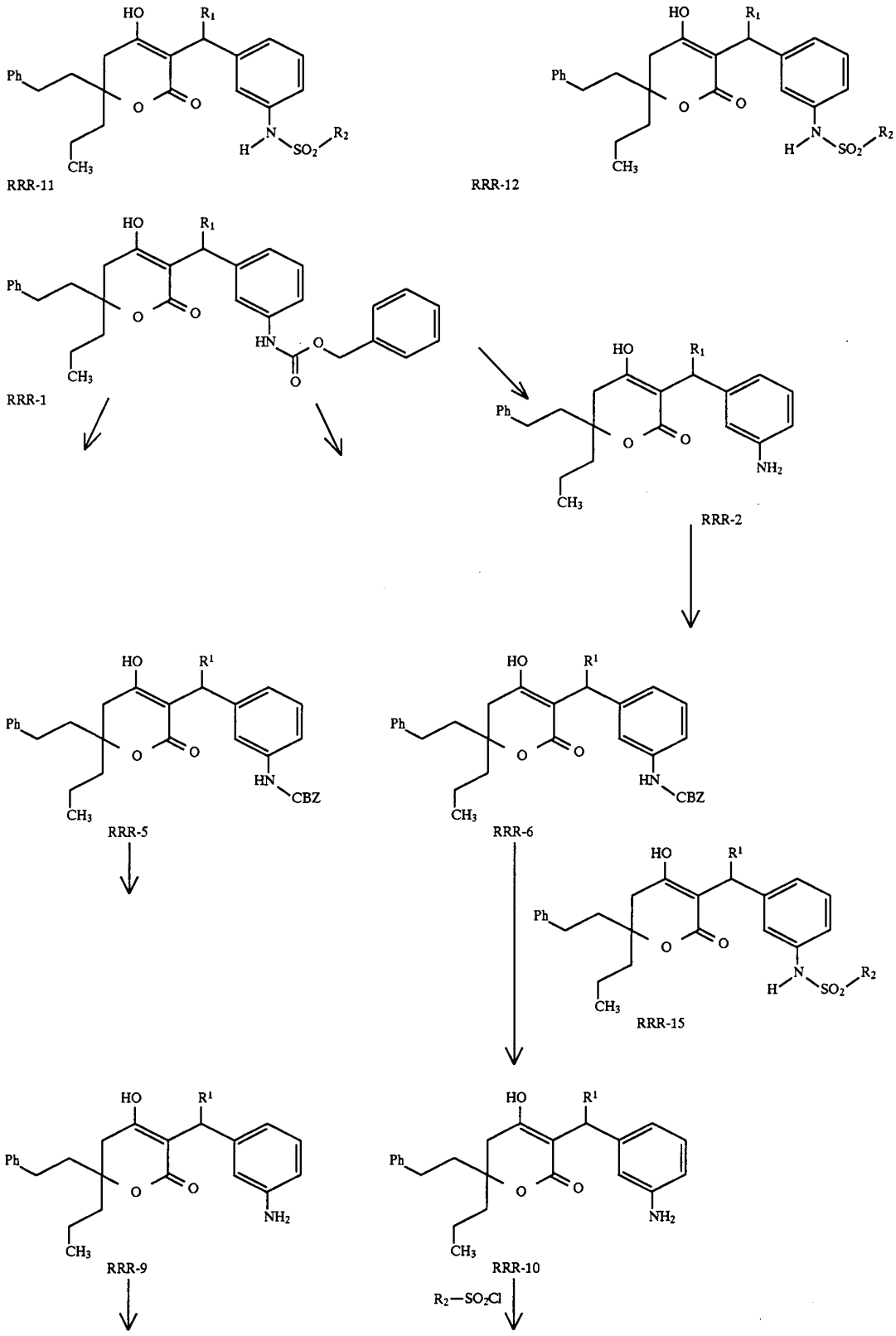

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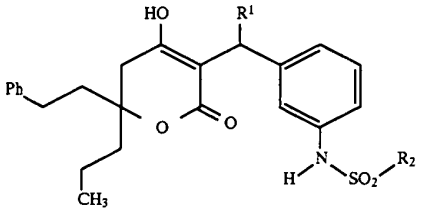

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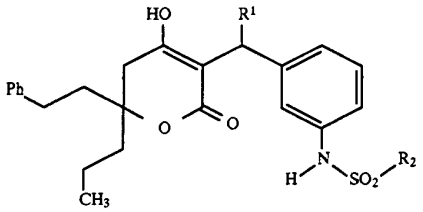

RRR-14

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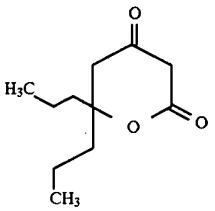

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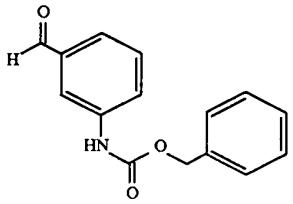

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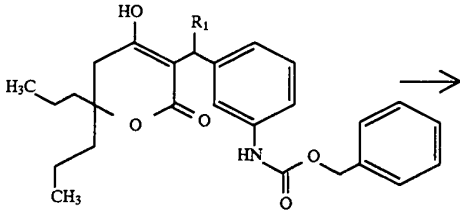

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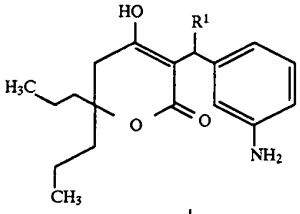

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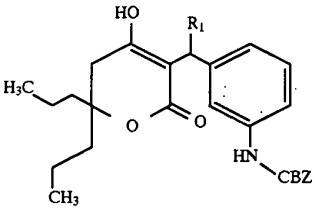

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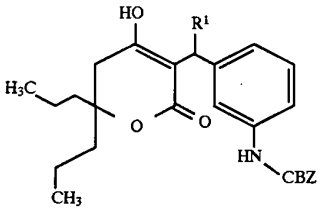

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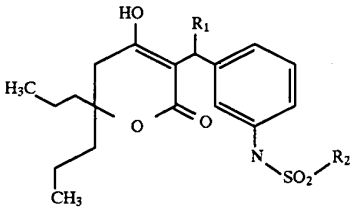

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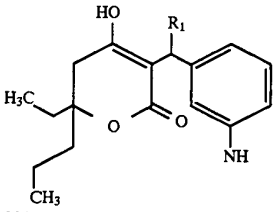

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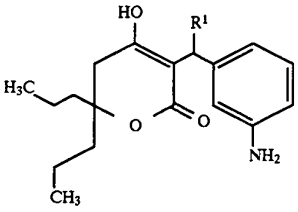
$R_2—SO_2Cl$



SSS-6

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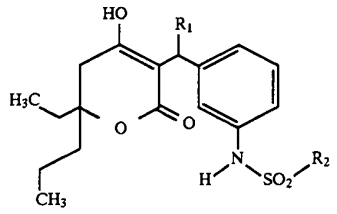
CHART SSS



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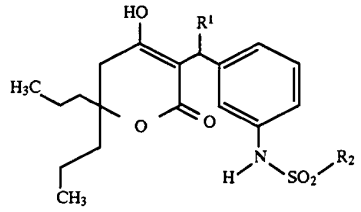
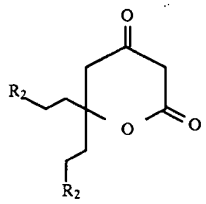


SSS-8

CHART TTT



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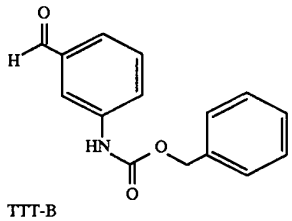

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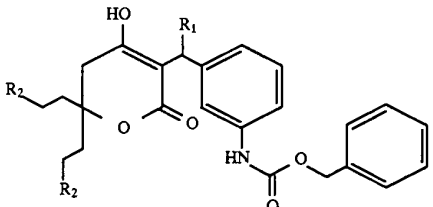

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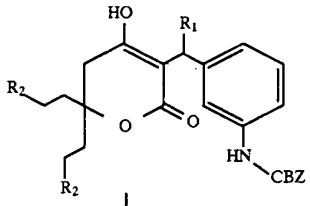

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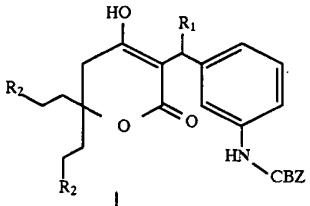

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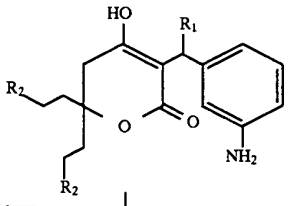

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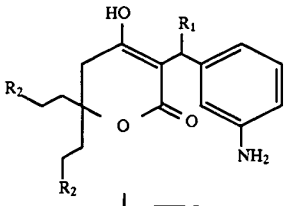

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R_3-SO_2Cl

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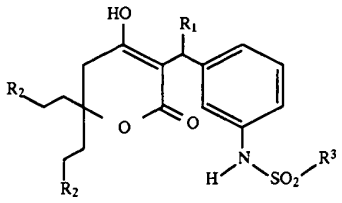

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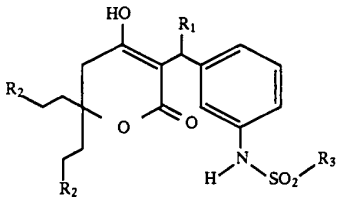

TTT-7

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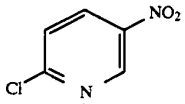

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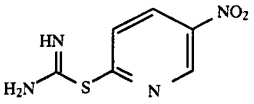

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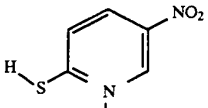

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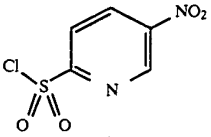

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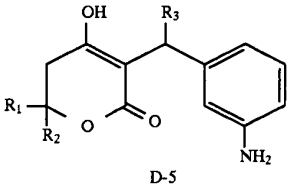

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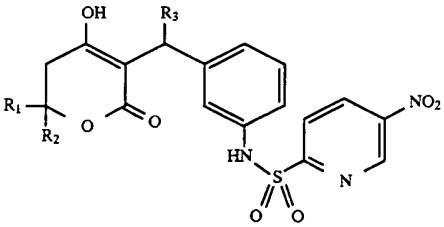

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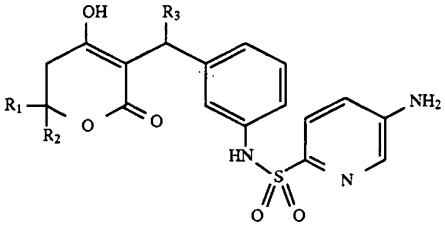

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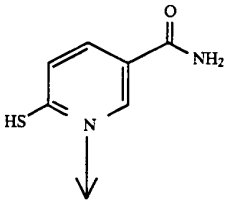

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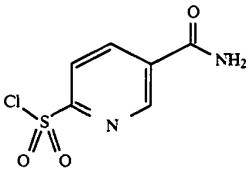

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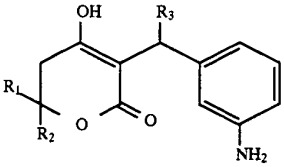

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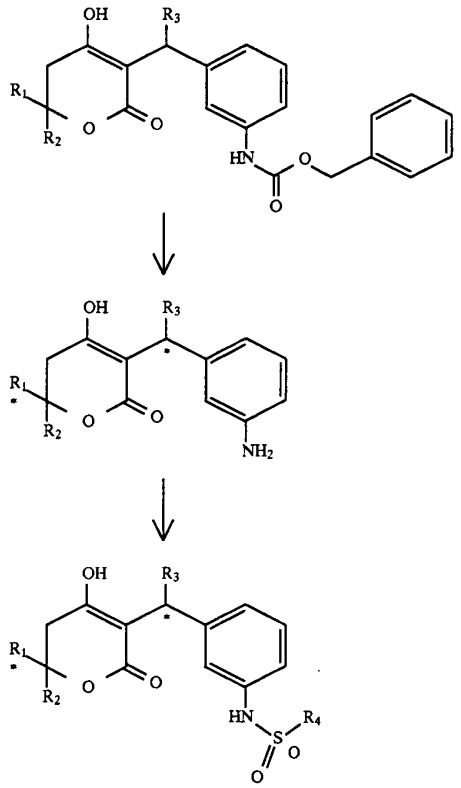

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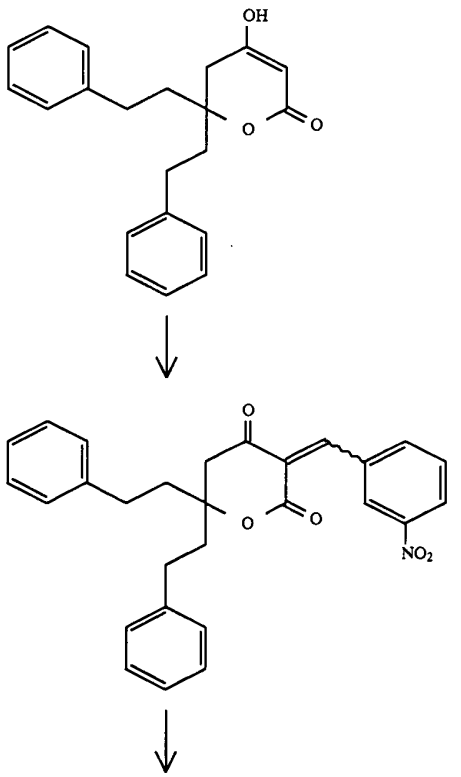

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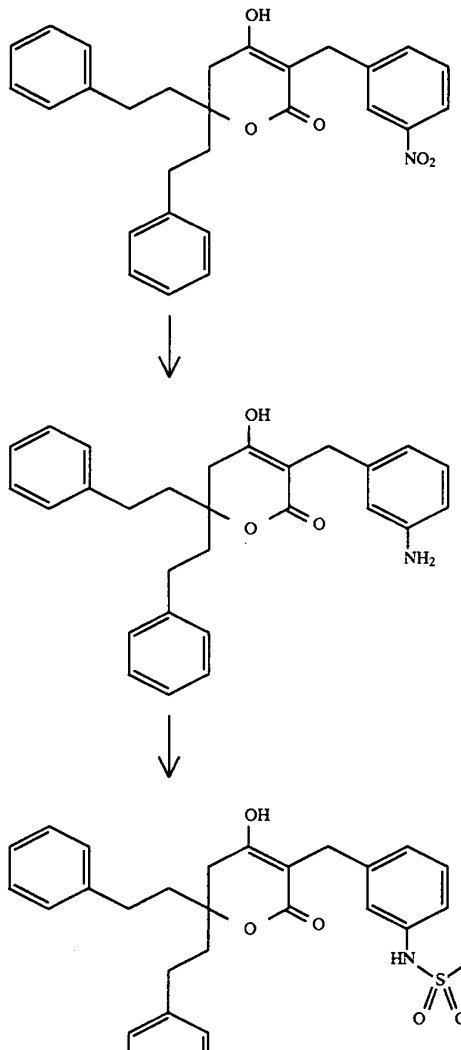

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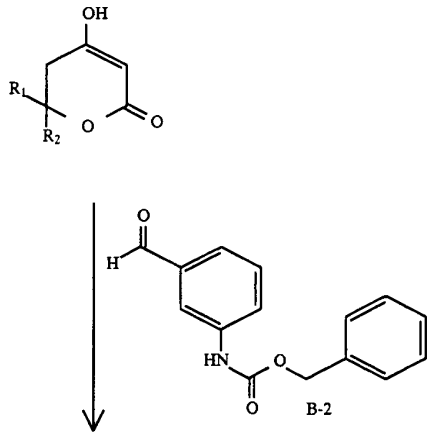

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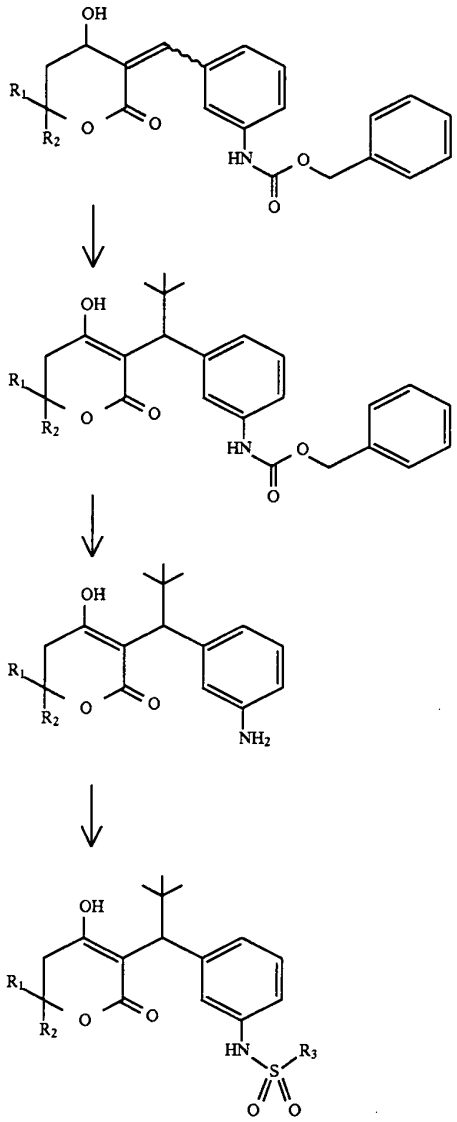

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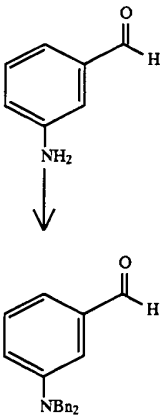

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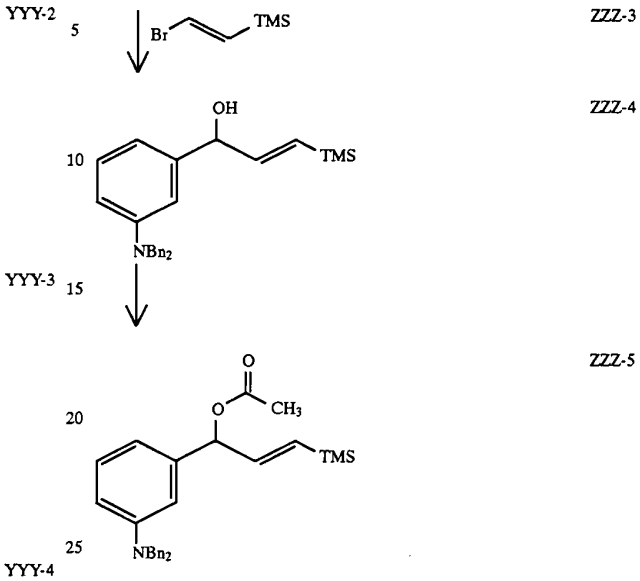

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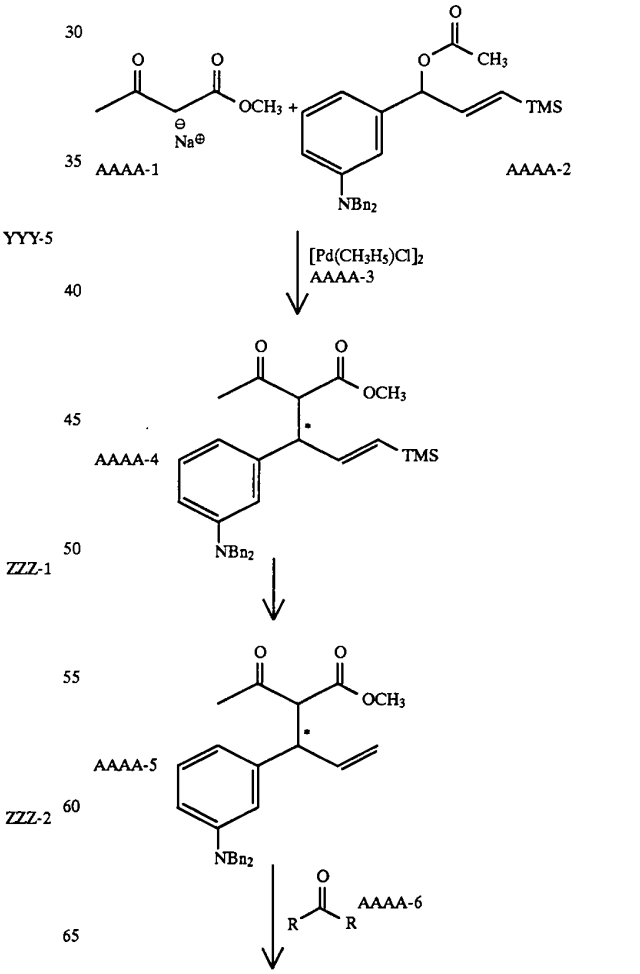

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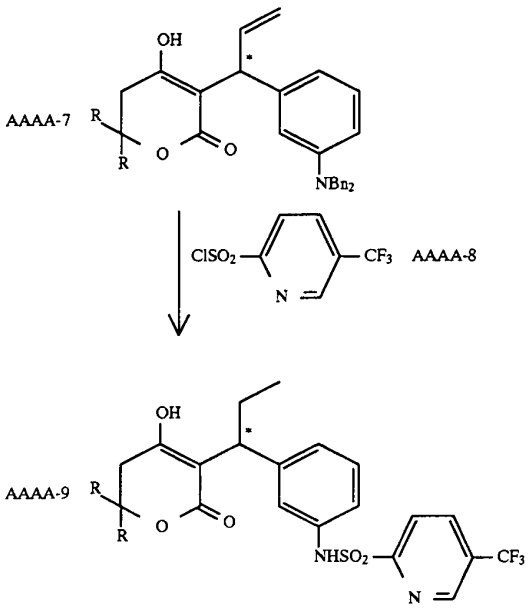

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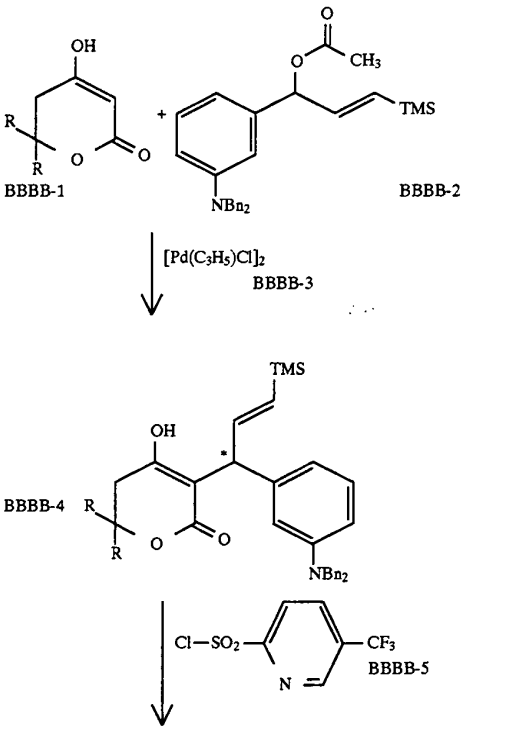

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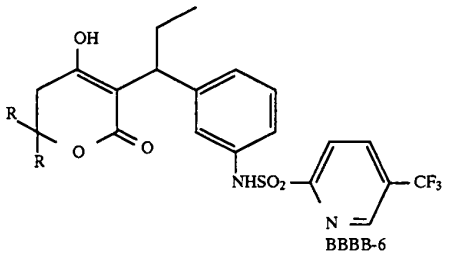

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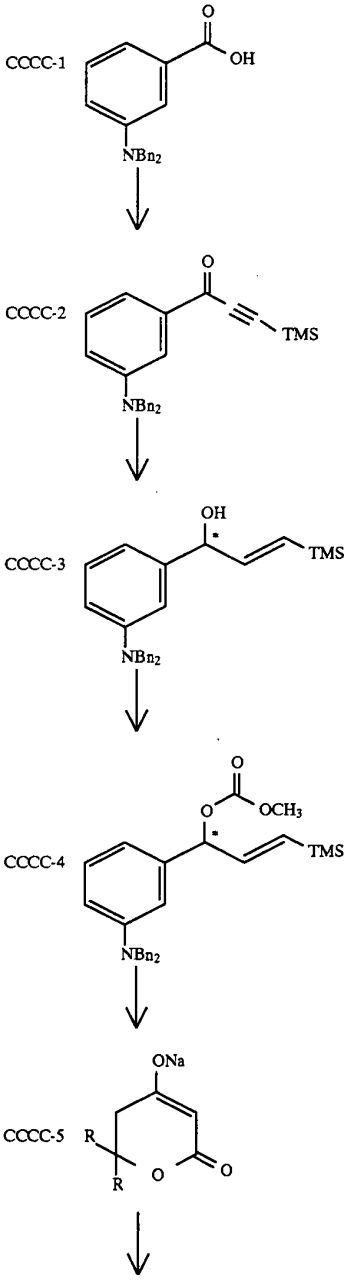

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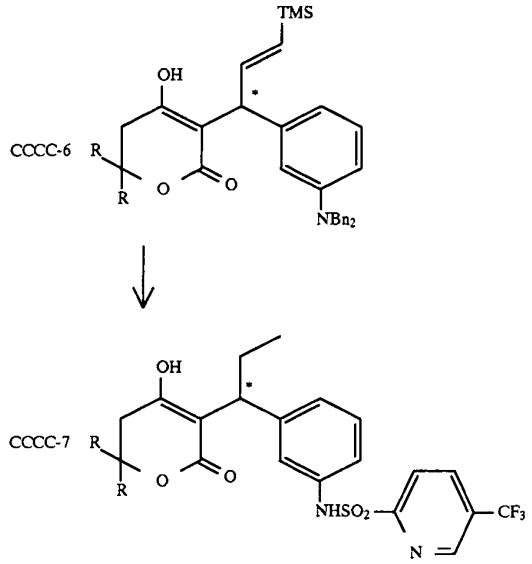

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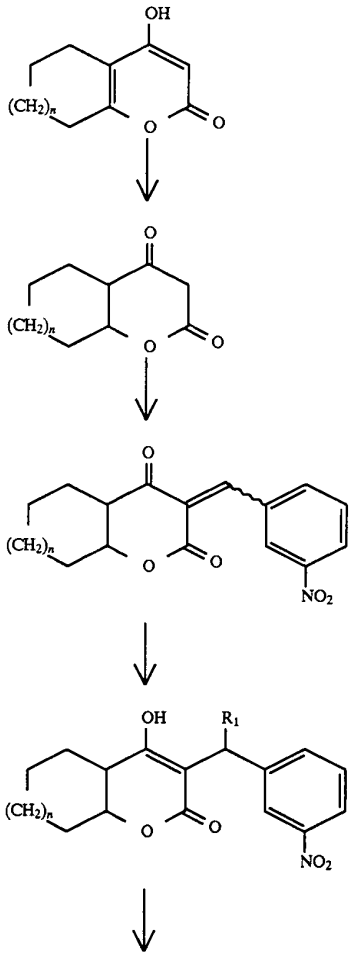

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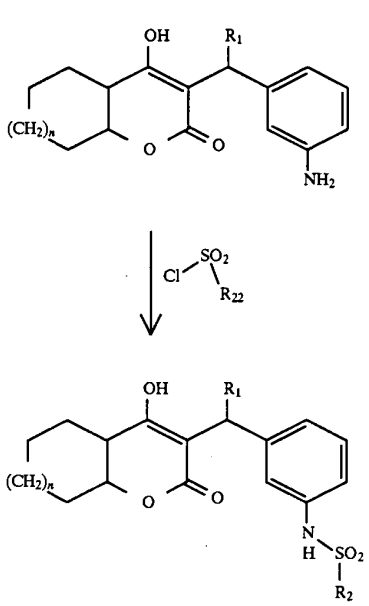

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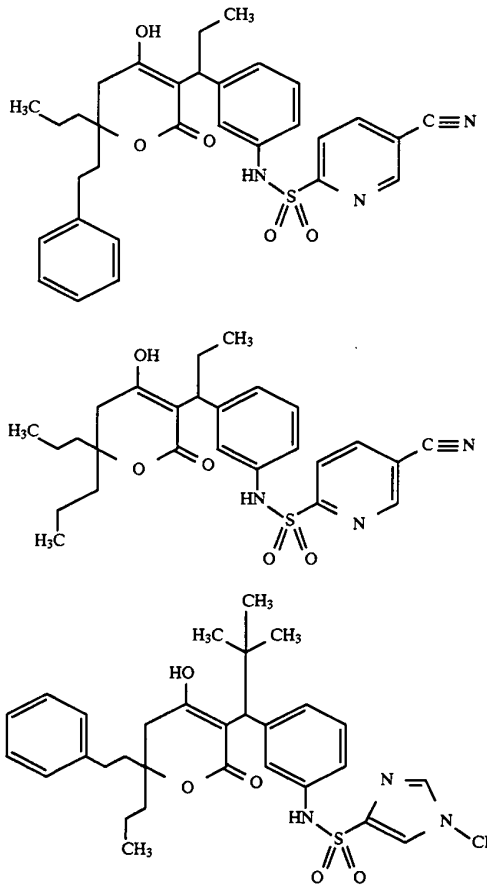

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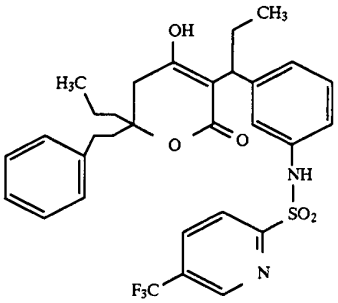
EEEE-4



EEEE-5

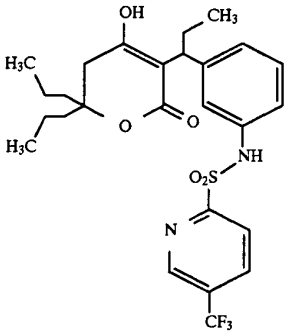


TABLE I

Compound of Example No.	HIV Protease FITC Assay Dose (uM)	Protease % Inhib	K_i (nM)
136	0.123	71.65	
	0.370	85.67	
	1.100	99.02	
	3.300	100.99	
	10.000	102.37	
	30.000	101.94	
			1.320
145A	0.123	108.66	
	0.370	111.34	
	1.100	118.54	
	3.300	115.43	
	10.000	113.05	
	30.000	114.19	
			1.100
137	0.123	98.83	
	0.370	91.54	
	1.100	100.7	
	3.300	109.9	
	10.000	98.17	
	30.000	93.82	
			0.520
			0.700
138	0.123	100.88	
	0.370	95.51	
	1.100	101.11	
	3.300	99.64	
	10.000	94.75	
	30.000	104.68	
			0.730
			1.400
97	0.123	104.87	
	0.370	106.06	
	1.100	110.44	
	3.300	106.67	
	10.000	115.76	
	30.000	115.47	
			1.000
98 First Compound			0.740

TABLE I-continued

Compound of Example No.	HIV Protease FITC Assay Dose (uM)	Protease % Inhib	K_i (nM)
			0.800
98 Second Compound			0.840
			0.800
139	0.123	98.33	
	0.370	101.22	
	1.100	104.71	
	3.300	99.3	
	10.000	99.28	
	30.000	102.85	
			1.890
140	0.123	103.22	
	0.370	96.01	
	1.100	107.37	
	3.800	112.51	
	10.000	112.53	
	30.000	119.14	
			1.440
40	0.123	59.6	
	0.370	101.71	
	1.100	98.73	
	3.300	105.16	
	10.000	88.7	
	30.000	72.74	
			10.800
41	0.123	103	
	0.370	102.38	
	1.100	103.92	
	3.300	100.93	
	10.000	85.88	
	30.000	72.79	
			3.170
44	0.123	98.43	
	0.370	114.5	
	1.100	119.79	
	3.300	112.7	
	10.000	101.66	
	30.000	80.02	
			1.800
145B	0.123	81.81	
	0.370	88.38	
	1.100	96.54	
	3.300	87.85	
	10.000	102.12	
	30.000	84.52	
			1.240
135	0.123	33.21	
	0.370	84.5	
	1.100	99.09	
	3.300	96.86	
	10.000	101.49	
	30.000	102.4	
			0.480
104	0.123	<10	
	0.370	61.68	
	1.100	81.78	
	3.300	93.28	
	10.000	96.4	
	30.000	109.22	
			1.600
48	0.123	111.37	
	0.370	103.64	
	1.100	110.44	
	3.300	89.27	
	10.000	110.97	
	30.000	105.44	
			0.520
49	0.123	111.16	
	0.370	119.71	
	1.100	120.17	
	3.300	106.02	
	10.000	108.34	
	30.000	112.5	
			0.960
50	0.123	100.54	

TABLE I-continued

Compound of Example No.	HIV Protease FITC Assay Dose (uM)	Protease % Inhib	K_i (nM)
	0.370	108.31	
	1.100	112.66	
	3.300	112.42	
	10.000	101.02	
	30.000	84.79	
			1.780
105	0.123	101.26	
	0.370	114.56	
	1.100	107.19	
	3.300	110.88	
	10.000	111.16	
	30.000	110.6	
			0.880
52	0.123	85.08	
	0.370	87.32	
	1.100	92.64	
	3.300	97.38	
	10.000	97.15	
	30.000	88.89	
			1.400
53	0.123	88.61	
	0.370	97.74	
	1.100	97.95	
	3.300	99.62	
	10.000	90.16	
	30.000	84.37	
			0.900
55	0.123	<10	
	0.370	18.77	
	1.100	58.27	
	3.300	86.98	
	10.000	98.33	
	30.000	85.88	
			1.700
107	0.123	92.69	
	0.370	99.24	
	1.100	105.15	
	3.300	103.44	
	10.000	110.33	
	30.000	103.47	
			0.890
			0.700
99	0.123	85.69	
	0.370	101.55	
	1.100	108.05	
	3.300	100.05	
	10.000	106.61	
	30.000	103.12	
			0.660
141	0.123	78.72	
	0.370	88.65	
	1.100	92.04	
	3.300	88.26	
	10.000	97.8	
	30.000	98.48	
			1.400
142	0.123	78.01	
	0.370	92.52	
	1.100	106.64	
	3.300	105.15	
	10.000	110.58	
	30.000	106.77	
			1.600
56	0.123	104.11	
	0.370	108.31	
	1.100	105.31	
	3.300	105.47	
	10.000	114.94	
	30.000	111.25	
			0.230
57	0.123	99.07	
	0.370	105.17	
	1.100	110.68	
	3.300	97.8	
	10.000	104.74	

TABLE I-continued

Compound of Example No.	HIV Protease FITC Assay Dose (uM)	Protease % Inhib	K_i (nM)
	30.000	115.02	
			0.360
58	0.123	64.87	
	0.370	83.71	
	1.100	94.24	
	3.300	95.88	
	10.000	100.27	
	30.000	89.81	
			3.800
59	0.123	76.69	
	0.370	90.54	
	1.100	101.9	
	8.300	99.87	
	10.000	105.16	
	30.000	102.02	
			3.500
60	0.123	73.03	
	0.370	94.3	
	1.100	101.28	
	3.300	100.84	
	10.000	105.68	
	30.000	107.38	
			0.950
61	0.123	86.83	
	0.370	95.51	
	1.100	103.35	
	3.300	102.54	
	10.000	105.61	
	30.000	103.53	
			0.710
93A	0.123	59.48	
	0.370	90.42	
	1.100	103.54	
	3.300	108.54	
	10.000	109.19	
	30.000	96.57	
			6.060
143	0.123	80.78	
	0.370	97.65	
	1.100	104.91	
	3.300	102.39	
	10.000	101.25	
	30.000	103.08	
			0.800
144	0.123	80.58	
	0.370	87.39	
	1.100	93.82	
	3.300	100.01	
	10.000	98.12	
	30.000	95.88	
			1.200
145	0.123	73.63	
	0.370	89.78	
	1.100	99.69	
	3.300	94.8	
	10.000	96.85	
	30.000	87.97	
			0.490
100	0.123	102.53	
	0.370	100.67	
	1.100	91.01	
	3.300	96.54	
	100.000	100.86	
	30.000	100.62	
			0.730
62	0.123	76.18	
	0.370	85.15	
	1.100	85.28	
	3.300	78.67	
	10.000	79.69	
	30.000	79.39	
			0.800
108	0.123	103.43	
	0.370	102.13	
	1.100	101.87	

TABLE I-continued

Compound of Example No.	HIV Protease FITC Assay Dose (uM)	Protease % Inhib	K_i (nM)
	3.300	102.41	
	10.000	107.73	
	30.000	106.39	
			0.160
109	0.123	105.42	
	0.370	99.35	
	1.100	103.75	
	3.300	100.96	
	10.000	108.56	
	30.000	109.31	
239	0.123	83.64	
	0.370	96.63	
	1.100	98.41	
	3.300	99.53	
	10.000	103.21	
	30.000	108.02	
			1.440
			0.860
152	0.123	11.52	
	0.370	80.2	
	1.100	95.79	
	3.300	94.43	
	10.000	95.45	
	30.000	96.47	
			0.710
8	0.123	99.23	
	0.370	110.11	
	1.100	102.93	
	3.300	110.02	
	10.000	105.11	
	30.000	101.91	
			0.350
9	0.123	99.09	
	0.370	103.78	
	1.100	104.9	
	3.300	104.69	
	10.000	107.08	
	30.000	107.87	
			0.420
10	0.123	102.17	
	0.370	111.74	
	1.100	115.65	
	3.300	119.47	
	10.000	128.59	
	30.000	130.05	
			5.710
151	0.123	111.03	
	0.370	114.59	
	1.100	117.62	
	3.300	118.9	
	10.000	116.34	
	30.000	114.87	
			0.360
153	0.123	81.27	
	0.370	91.11	
	1.100	100.49	
	3.300	104.76	
	10.000	102.76	
	30.000	100.71	
			1.850
154	0.123	99.8	
	0.370	98.17	
	1.100	99.52	
	3.300	97.59	
	10.000	103.54	
	30.000	99.18	
			0.220
240	0.123	96.32	
	0.370	100.98	
	1.100	102.71	
	3.300	101.88	
	10.000	104.28	
	30.000	107.17	
			1.300
1	0.123	75.4	

TABLE I-continued

Compound of Example No.	HIV Protease FITC Assay Dose (uM)	Protease % Inhib	K_i (nM)
	0.370	87.3	
	1.100	97.1	
	3.300	96.76	
	10.000	99.68	
	30.000	97.43	
			15.000
101	0.123	70.24	
	0.370	83.98	
	1.100	93.35	
	3.300	97.01	
	10.000	102.48	
	30.000	97.35	
			0.660
146	0.123	68.12	
	0.370	87.38	
	1.100	103.18	
	3.300	103.26	
	10.000	102.54	
	30.000	101.95	
			0.690
147	0.123	77.45	
	0.370	102.86	
	1.100	111.6	
	3.300	110.34	
	10.000	114.04	
	30.000	108.28	
			1.000
110	0.123	77.89	
	0.370	82.72	
	1.100	95.11	
	3.300	99.1	
	10.000	99.22	
	30.000	101.27	
			3.260
			3.630
102	0.123	87.11	
	0.370	92.73	
	1.100	102.21	
	3.300	110.44	
	10.000	116.72	
	30.000	107.83	
			0.700
103	0.123	65.51	
	0.370	82.58	
	1.100	96.86	
	3.300	100.29	
	10.000	104.76	
	30.000	96.05	
			1.720
194	0.123	<10	
	0.370	20.03	
	1.100	53.89	
	3.300	75.23	
	10.000	85.48	
	30.000	85.18	
195	0.123	60.89	
	0.370	85.08	
	1.100	90.79	
	3.300	90.83	
	10.000	93.14	
	30.000	92.69	
			3.700
150	0.123	78.42	
	0.370	96.45	
	1.100	100.07	
	3.300	102.81	
	10.000	106.88	
	30.000	109.34	
			5.900
148	0.123	81.35	
	0.370	91.68	
	1.100	95.57	
	3.300	90.04	
	10.000	99.17	
	30.000	93.52	

TABLE I-continued

Compound of Example No.	HIV Protease FITC Assay Dose (uM)	Protease % Inhib	K_i (nM)
			4.770
			18.100
149	0.123	80.51	
	0.370	87.52	
	1.100	96.32	
	3.300	92.86	
	10.000	97.12	
	30.000	95.99	
			3.410
			62.700
94	0.123	75.76	
	0.370	106.6	
	1.100	107.3	
	3.300	104.91	
	10.000	109.2	
	30.000	111.29	
			16.370
95	0.123	91.2	
	0.370	102.33	
	1.100	105.86	
	3.300	112.79	
	10.000	110.04	
	30.000	112.69	
			5.350
96	0.123	94.17	
	0.370	119.36	
	1.100	122.12	
	3.300	111	
	10.000	111.32	
	30.000	109.23	
			5.300
42	0.123	86.15	
	0.370	102.71	
	1.100	98.26	
	3.300	102.4	
	10.000	91.43	
	30.000	76.12	
			3.100
43	0.123	85.63	
	0.370	99.01	
	1.100	95.68	
	3.300	96.68	
	10.000	101.58	
	30.000	85.57	
			3.650
45	0.123	82.22	
	0.370	94.37	
	1.100	101.04	
	3.300	103.16	
	10.000	89.76	
	30.000	67.5	
			4.780
46	0.123	85.86	
	0.370	99.19	
	1.100	103.31	
	3.300	97.62	
	10.000	91.45	
	30.000	74.13	
			2.920
47	0.123	66.3	
	0.370	86.79	
	1.100	94.7	
	3.300	100.95	
	10.000	98.68	
	30.000	84.45	
			3.000
			2.980
51	0.123	98.71	
	0.370	103.68	
	1.100	104.78	
	3.300	101.27	
	10.000	95.07	
	30.000	79.72	
			2.660
106	0.123	60.94	

TABLE I-continued

Compound of Example No.	HIV Protease FITC Assay Dose (uM)	Protease % Inhib	K_i (nM)
	0.370	86.56	
	1.100	93.7	
	3.300	98.88	
	10.000	99.03	
	30.000	106.06	
			3.290
54	0.123	46.64	
	0.370	72.41	
	1.100	87.91	
	3.300	89.11	
	10.000	87.77	
	30.000	91.99	
			13.300
146	10.000	102.54	
	30.000	101.95	
			0.690
192	0.123	44.04	
	0.370	76.28	
	1.100	93.96	
	3.300	96.93	
	10.000	103.33	
	30.000	94.38	
			7.200
193	0.123	18.42	
	0.370	40.3	
	1.100	77.74	
	3.300	98.1	
	10.000	108.41	
	30.000	103.17	
			35.000
11	0.123	78.93	
	0.370	95.26	
	1.100	100.26	
	3.300	95.12	
	10.000	99.66	
	30.000	104.39	
			1.900
12	0.123	75.65	
	0.370	87.16	
	1.100	91.79	
	3.300	91.11	
	10.000	94.74	
	30.000	95.69	
			2.150
13	0.123	68.94	
	0.370	88.07	
	1.100	93.98	
	3.300	95.51	
	10.000	98.61	
	30.000	104.2	
			4.150
14	0.123	65.67	
	0.370	87.96	
	1.100	96.79	
	3.300	96.56	
	10.000	101.77	
	30.000	106.39	
			6.880
15	0.123	77.63	
	0.370	88.45	
	1.100	92.44	
	3.300	94.03	
	10.000	95.84	
	30.000	99.23	
			2.800
63	0.123	68.88	
	0.370	79.56	
	1.100	88.58	
	3.300	87.44	
	10.000	83.58	
	30.000	78.84	
64	0.123	27.95	
	0.370	50.83	
	1.100	75.60	
	3.300	80.88	

TABLE I-continued

Compound of Example No.	HIV Protease FITC Assay Dose (uM)	Protease % Inhib	K_i (nM)
	10.000	82.03	
	30.000	84.39	
250			1.2
261			0.87
260			2.0
258			4.3
259			2.2
256			8.3
257			9.0
246			1.7
247			1.2
254			3.0
255			1.6
248			4.7
249			0.75
251	0.123	70.84	
	0.370	90.56	
	1.100	97.68	
	3.300	94.5	
	10.000	94.16	
	30.000	93.24	
			1.9
253	0.123	94.03	
	0.370	96.84	
	1.100	97.64	
	3.300	95.93	
	10.000	96.95	
	30.000	98.52	
252	0.123	69.96	
	0.370	85.05	
	1.100	89.69	
	3.300	100.57	
	10.000	96.21	
	30.000	91.38	
			1.6
262	0.123	91.8	
	0.370	96.6	
	1.100	97.13	
	3.300	95.4	
	10.000	94.17	
	30.000	89.18	
263	0.123	98.08	
	0.370	98.99	
	1.100	99.1	
	3.300	98.08	
	10.000	96.21	
	30.000	88.19	
264	0.123	67.18	
	0.370	75.01	
	1.100	67.71	
	3.300	57.62	
	10.000	53.69	
	30.000	64.58	
			3.7
265	0.123	33.23	
	0.370	56.33	
	1.100	57.78	
	3.300	63.69	
	10.000	80.29	
	30.000	85.64	
			1.0

TABLE II

EXAMPLE NUMBER	ENZYME	DOSE	PROTEASE % INHIB.	FITC KI (NM)
280	HIV-1	0.123	95.28	
	HIV-1	0.370	94.98	
	HIV-1	1.100	93.01	
	HIV-1	3.300	86.69	
	HIV-1	10.000	78.64	

TABLE II-continued

EXAMPLE NUMBER	ENZYME	DOSE	PROTEASE % INHIB.	FITC KI (NM)
	HIV-1	30.000	76.85	
	HIV1TANDEM			0.100
293	HIV-1	0.123	53.45	
	HIV-1	0.370	77.51	
	HIV-1	1.100	94.18	
	HIV-1	3.300	103.03	
	HIV-1	10.000	97.41	
	HIV-1	30.000	92.01	4.300
295	HIV1TANDEM			0.071
281	HIV1TANDEM			0.002
	HIV1TANDEM			0.004
285	HIV1TANDEM			0.015
	HIV-1	0.123	81.8	
	HIV-1	0.370	95.8	
	HIV-1	1.100	99.11	
	HIV-1	3.300	109.33	
	HIV-1	10.000	104.61	
	HIV-1	30.000	86.84	
286	HIV1TANDEM			13.300
	HIV-1	0.123	34.76	
	HIV-1	0.370	68.74	
	HIV-1	1.100	89.29	
	HIV-1	3.300	93.11	
	HIV-1	10.000	108.17	
	HIV-1	30.000	95.31	
287	HIV1TANDEM			0.038
283	HIV1TANDEM			0.004
296	HIV1TANDEM			0.042
291	HIV1TANDEM			0.012
	HIV1TANDEM			0.026
289	HIV1TANDEM			0.133
290	HIV1TANDEM			1.880
298	HIV1TANDEM			0.004
	HIV1TANDEM			0.003
	HIV1TANDEM			0.007
266	HIV1TANDEM			0.033
272	HIV1TANDEM			3.600
270	HIV1TANDEM			0.024
	HIV-1	0.123	75.26	
	HIV-1	0.370	85.62	
	HIV-1	1.100	93.45	
	HIV-1	3.300	96.62	
	HIV-1	10.000	94.57	
	HIV-1	30.000	82.67	
273	HIV1TANDEM			2.300
	HIV-1	0.123	< 10	
	HIV-1	0.370	23.24	
	HIV-1	1.100	75.38	
	HIV-1	3.300	94.63	
	HIV-1	10.000	95.93	
	HIV-1	30.000	91	
276	HIV1TANDEM			33.000
	HIV-1	0.123	16.49	
	HIV-1	0.370	38.95	
	HIV-1	1.100	66.1	
	HIV-1	3.300	90.01	
	HIV-1	10.000	90.97	
	HIV-1	30.000	87.6	
278	HIV1TANDEM			0.040
	HIV-1	0.123	76.76	
	HIV-1	0.370	86.99	
	HIV-1	1.100	95.6	
	HIV-1	3.300	96.91	
	HIV-1	10.000	93.32	
	HIV-1	30.000	86.18	
268	HIV1TANDEM			0.835
271	HIV1TANDEM			0.051
299	HIV-1	0.123	83.51	
	HIV-1	0.370	104.76	
	HIV-1	1.100	117.95	
	HIV-1	3.300	115.61	
	HIV-1	10.000	128.03	
	HIV-1	30.000	102.89	
	HIV1TANDEM			0.200
300	HIVTANDEM			0.100
	HIVTANDEM			0.100

TABLE II-continued

EXAMPLE NUMBER	ENZYME	DOSE	PROTEASE % INHIB.	FITC KI (NM)
	HIV-1	0.123	90.61	
	HIV-1	0.370	99.05	
	HIV-1	1.100	111.45	
	HIV-1	3.300	109.19	
	HIV-1	10.000	105.56	
	HIV-1	30.000	104.91	
302	HIVTANDEM			1.870
	HIVTANDEM			3.600
	HIV-1	0.123	38	
	HIV-1	0.370	65.57	
	HIV-1	1.100	89.51	
	HIV-1	3.300	118.39	
	HIV-1	10.000	104.49	
	HIV-1	30.000	92.16	
304	HIV-1	0.123	92.01	
	HIV-1	0.370	93.28	
	HIV-1	1.100	96.47	
	HIV-1	3.300	100.47	
	HIV-1	10.000	107.61	
	HIV-1	30.000	79.68	
	HIV1TANDEM			0.100
	HIV1TANDEM			0.050
305	HIV-1	0.123	99.99	
	HIV-1	0.370	110.76	
	HIV-1	1.100	114.35	
	HIV-1	3.300	110.88	
	HIV-1	10.000	102.01	
	HIV-1	30.000	57.83	
	HIV1TANDEM			0.400
306	HIV-1	0.123	71.79	
	HIV-1	0.370	82.71	
	HIV-1	1.100	89.3	
	HIV-1	3.300	97.29	
	HIV-1	10.000	82.59	
	HIV-1	30.000	53.43	
	HIV1TANDEM			0.040
307	HIV-1	0.123	77.39	
	HIV-1	0.370	99.85	
	HIV-1	1.100	107.87	
	HIV-1	3.300	93.34	
	HIV-1	10.000	83.49	
	HIV-1	30.000	69.74	
	HIV1TANDEM			0.072
308	HIV-1	0.123	75.06	
	HIV-1	0.370	108.14	
	HIV-1	1.100	95.01	
	HIV-1	3.300	108.43	
	HIV-1	10.000	110.75	
	HIV-1	30.000	96.28	
	HIV1TANDEM			0.074
310	HIV-1	0.123	16.81	
	HIV-1	0.370	50.11	
	HIV-1	1.100	78.69	
	HIV-1	3.300	100.22	
	HIV-1	10.000	124.77	
	HIV-1	30.000	110.91	
	HIV1TANDEM			1.500
311	HIV-1	0.123	86.51	
	HIV-1	0.370	91.49	
	HIV-1	1.100	101.8	
	HIV-1	3.300	96.5	
	HIV-1	10.000	93.77	
	HIV-1	30.000	77.63	
	HIV1TANDEM			0.007
312	HIV1TANDEM			0.255
314	HIV1TANDEM			0.700
	HIV-1	0.123	82.92	
	HIV-1	0.370	96.14	
	HIV-1	1.100	114.86	
	HIV-1	3.300	100.76	
	HIV-1	10.000	88.75	
	HIV-1	30.000	73.42	
315	HIV1TANDEM			0.029
	HIV-1	0.123	79.95	
	HIV-1	0.370	87.25	
	HIV-1	1.100	88.08	

TABLE II-continued

EXAMPLE NUMBER	ENZYME	DOSE	PROTEASE % INHIB.	FITC KI (NM)
	HIV-1	3.300	97.03	
	HIV-1	10.000	100.2	
	HIV-1	30.000	106.4	
316	HIV1TANDEM			0.357
	HIV-1	0.123	75.49	
	HIV-1	0.370	85.02	
	HIV-1	1.100	100.32	
	HIV-1	3.300	95.46	
	HIV-1	10.000	99.71	
	HIV-1	30.000	87.91	
317	HIV1TANDEM			0.040
	HIV-1	0.123	87.38	
	HIV-1	0.370	94.14	
	HIV-1	1.100	98.45	
	HIV-1	3.300	95.97	
	HIV-1	10.000	101.26	
	HIV-1	30.000	108.59	
318	HIV1TANDEM			0.019
	HIV-1	0.123	98.06	
	HIV-1	0.370	106.35	
	HIV-1	1.100	101.88	
	HIV-1	3.300	88.73	
	HIV-1	10.000	94.49	
	HIV-1	30.000	82.83	
319	HIV1TANDEM			29.500
	HIV-1	0.123	10.75	
	HIV-1	0.370	32.65	
	HIV-1	1.100	60.14	
	HIV-1	3.300	75.86	
	HIV-1	10.000	93.46	
	HIV-1	30.000	74.48	
320	HIV1TANDEM			0.071
	HIV1TANDEM			0.050
	HIV1TANDEM			0.075
322	HIV1TANDEM			1.070
	HIV1TANDEM			1.290
324	HIV1TANDEM			0.156
326	HIV1TANDEM			0.029
328	HIV-1			22.000
	HIV-1	0.123	27.81	
	HIV-1	0.370	79.47	
	HIV-1	1.100	95.45	
	HIV-1	3.300	96.77	
	HIV-1	10.000	96.78	
	HIV-1	30.000	92.17	
329	HIV-1			12.000
	HIV-1	0.123	46.4	
	HIV-1	0.370	88.19	
	HIV-1	1.100	96.63	
	HIV-1	3.300	100.32	
	HIV-1	10.000	97.07	
	HIV-1	30.000	96.35	
330	HIV1TANDEM			0.524
	HIV-1	0.123	93.74	
	HIV-1	0.370	94.32	
	HIV-1	1.100	93.66	
	HIV-1	3.300	85.63	
	HIV-1	10.000	87.9	
	HIV-1	30.000	69.82	
331	HIV1TANDEM			0.272
	HIV-1	0.123	99.76	
	HIV-1	0.370	104.06	
	HIV-1	1.100	108.51	
	HIV-1	3.300	99.3	
	HIV-1	10.000	103.28	
	HIV-1	30.000	93.3	
332	HIV1TANDEM			0.400
	HIV-1	0.123	81.87	
	HIV-1	0.370	85.65	
	HIV-1	1.100	86.23	
	HIV-1	3.300	93.28	
	HIV-1	10.000	91.68	
	HIV-1	30.000	95.08	
	HIV-1			1.600
333	HIV-1	0.123	66.73	
	HIV-1	0.370	85.07	

TABLE II-continued

EXAMPLE NUMBER	ENZYME	DOSE	PROTEASE % INHIB.	FITC KI (NM)
	HIV-1	1.100	85.12	
	HIV-1	3.300	93.69	
	HIV-1	10.000	89.38	
	HIV-1	30.000	77.91	
	HIV-1			7.700
334	HIV1TANDEM			0.450
	HIV-1	0.123	93.49	
	HIV-1	0.370	90.25	
	HIV-1	1.100	94.57	
	HIV-1	3.300	102.47	
	HIV-1	10.000	97.61	
	HIV-1	30.000	96.3	
335	HIV-1	0.123	60.07	
	HIV-1	0.370	99.75	
	HIV-1	1.100	97.05	
	HIV-1	3.300	92.06	
	HIV-1	10.000	89.77	
	HIV-1	30.000	76.25	
	HIV1TANDEM			0.040
336	HIV-1	0.123	65.64	
	HIV-1	0.370	112	
	HIV-1	1.100	89.54	
	HIV-1	3.300	88.06	
	HIV-1	10.000	77.12	
	HIV-1	30.000	62.28	
	HIV1TANDEM			0.032
338	HIV-1	0.123	61.74	
	HIV-1	0.370	85.32	
	HIV-1	1.100	80.46	
	HIV-1	3.300	89.62	
	HIV-1	10.000	83.53	
	HIV-1	30.000	62.34	
	HIV1TANDEM			0.100
339	HIV-1	0.123	83.49	
	HIV-1	0.370	100.6	
	HIV-1	1.100	101.42	
	HIV-1	3.300	104.71	
	HIV-1	10.000	91.38	
	HIV-1	30.000	72.86	
	HIV1TANDEM			0.120
340	HIV-1	0.123	80.58	
	HIV-1	0.370	90.49	
	HIV-1	1.100	90.16	
	HIV-1	3.300	91.57	
	HIV-1	10.000	89.49	
	HIV-1	30.000	71.99	
	HIV1TANDEM			0.060
342	HIV-1	0.123	81.06	
	HIV-1	0.370	93.18	
	HIV-1	1.100	96.94	
	HIV-1	3.300	85.55	
	HIV-1	10.000	73.55	
	HIV-1	30.000	73.95	
	HIV1TANDEM			0.309
343	HIV-1	0.123	57.5	
	HIV-1	0.370	76.83	
	HIV-1	1.100	81.02	
	HIV-1	3.300	86.43	
	HIV-1	10.000	60.56	
	HIV-1	30.000	46	2.900
344	HIV-1	0.123	47.37	
	HIV-1	0.370	72.84	
	HIV-1	1.100	81.17	
	HIV-1	3.300	83.08	
	HIV-1	10.000	68.47	
	HIV-1	30.000	46.24	5.900
345	HIV1TANDEM			0.032
	HIV-1	0.123	69.19	
	HIV-1	0.370	94.37	
	HIV-1	1.100	101.67	
	HIV-1	3.300	99.08	
	HIV-1	10.000	97.43	
	HIV-1	30.000	84.56	
347	HIV1TANDEM			13.600
	HIV-1	0.123	20.99	
	HIV-1	0.370	50.82	

TABLE II-continued

EXAMPLE NUMBER	ENZYME	DOSE	PROTEASE % INHIB.	FITC KI (NM)
	HIV-1	1.100	71.4	
	HIV-1	3.300	83	
	HIV-1	10.000	90.97	
	HIV-1	30.000	87.18	
348	HIV1TANDEM			1.960
	HIV-1	0.123	53.47	
	HIV-1	0.370	78.32	
	HIV-1	1.100	89.84	
	HIV-1	3.300	92.96	
	HIV-1	10.000	96.28	
	HIV-1	30.000	84.67	
349	HIV1TANDEM			0.111
	HIV-1	0.123	74.5	
	HIV-1	0.370	88.21	
	HIV-1	1.100	99.92	
	HIV-1	3.300	104.99	
	HIV-1	10.000	103.49	
	HIV-1	30.000	98.24	
351	HIV-1	0.123	< 10	
	HIV-1	0.370	< 10	
	HIV-1	1.100	25.4	
	HIV-1	3.300	55.11	
	HIV-1	10.000	78.53	
	HIV-1	30.000	90.55	
	HIV-1			558.000
352	HIV-1	0.123	< 10	
	HIV-1	0.370	25.31	
	HIV-1	1.100	47.78	
	HIV-1	3.300	74.99	
	HIV-1	10.000	85.86	
	HIV-1	30.000	87.82	
	HIV-1			168.000
353	HIV-1			10.400
	HIV1TANDEM			5.300
	HIV-1	0.123	51.83	
	HIV-1	0.370	68.49	
	HIV-1	1.100	70.71	
	HIV-1	3.300	63.96	
	HIV-1	10.000	51.8	
	HIV-1	30.000	43.93	
354	HIV-1	0.123	< 10	
	HIV-1	0.370	10.37	
	HIV-1	1.100	26.79	
	HIV-1	3.300	46.1	
	HIV-1	10.000	54.97	
	HIV-1	30.000	54.5	
	HIV-1			665.000
355	HIV-1			700.000
	HIV-1	0.123	< 10	
	HIV-1	0.370	< 10	
	HIV-1	1.100	< 10	
	HIV-1	3.300	20.72	
	HIV-1	10.000	46.66	
	HIV-1	30.000	67.82	
356	HIV1TANDEM			1.100
	HIV-1	0.123	54.96	
	HIV-1	0.370	71.75	
	HIV-1	1.100	90.19	
	HIV-1	3.300	92.28	
	HIV-1	10.000	100.22	
	HIV-1	30.000	95.16	
357	HIV1TANDEM			48.500
359	HIV1TANDEM			16.400
363	HIV1TANDEM			0.083
365	HIV1TANDEM			0.023
368	HIV1TANDEM			0.232
370	HIV-1	0.123	92.81	
	HIV-1	0.370	87.87	
	HIV-1	1.100	102.89	
	HIV-1	3.300	109.33	
	HIV-1	10.000	113.79	
	HIV-1	30.000	98.14	0.590
	HIV1TANDEM			0.050
	HIV-2			0.050
371	HIV-1	0.123	39.84	
	HIV-1	0.370	72.94	

TABLE II-continued

EXAMPLE NUMBER	ENZYME	DOSE	PROTEASE % INHIB.	FITC KI (NM)
	HIV-1	1.100	91.61	
	HIV-1	3.300	104.12	
	HIV-1	10.000	102.7	
	HIV-1	30.000	107.21	15.400
372	HIV-1	0.123	43.52	
	HIV-1	0.370	86.68	
	HIV-1	1.100	101.52	
	HIV-1	3.300	99.56	
	HIV-1	10.000	97.81	
	HIV-1	30.000	106.18	4.000
373	HIV-1	0.123	90.71	
	HIV-1	0.370	90.35	
	HIV-1	1.100	103.83	
	HIV-1	3.300	88.72	
	HIV-1	10.000	85.75	
	HIV-1	30.000	89.53	
	HIV1TANDEM			0.200
374	HIV1TANDEM	0.123	78.97	
		0.370	82.14	
		1.100	84.98	
		3.300	87.70	
		10.000	95.25	
		30.000	80.11	0.031

TABLE 3

U-No.	MS data	Name	Origin
300	587.2453 (EI)	5-Cyano-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide	Single stereoisomer; Derived from Isomer 1 of Preparation 143
301	587.2458 (EI)	5-Cyano-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide	Single stereoisomer; Derived from Isomer 2 of Preparation 143
302	587.2444 (EI)	5-Cyano-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide	Single stereoisomer; Derived from Isomer 3 of Preparation 143
303	587.2446 (EI)	5-Cyano-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl)-2-pyridinesulfonamide	Single stereoisomer; Derived from Isomer 4 of Preparation 143
304	525.2311 (EI)	5-Cyano-N-[3-(1-[5,6-dihydro-6,6-diisobutyl-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide	Racemic mixture
305	532.2856 (FAB)	N-[3-(1-[5,6-Dihydro-6,6-diisobutyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-1-methyl-1H-imidazole-4-sulfonamide	Racemic mixture
306	554.2688 (FAB)	5-Cyano-N-[3-(1-[5,6-dihydro-6,6-diisobutyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide	Racemic mixture
307	565.2607 (EI)	N-[3(R or S)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(R or S)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide	Single stereoisomer; Derived from Isomer 1 of Preparation 143
308	565.2629 (EI)	N-[3(R or S)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(R or S)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide	Single stereoisomer; Derived from Isomer 2 of Preparation 143

TABLE 3-continued

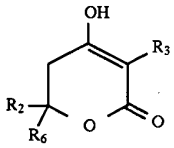
U-No.	MS data	Name	Origin
309	565.2605 (EI)	N-[3(R or S)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(R or S)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide	Single stereoisomer; Derived from Isomer 3 of Preparation 143
310	565.2626 (EI)	N-[3(R or S)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(R or S)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide	Single stereoisomer; Derived from Isomer 4 of Preparation 148
311	571.2113 (EI)	5-Cyano-N-[3-(1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]cyclopropyl-methyl)phenyl]-2-pyridine-sulfonamide	Diastereomeric mixture
312	577.2630 (EI)	5-Amino-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide	Single stereoisomer; Prepared from amine of Preparation 138 (derived from Isomer 1 of Preparation 143)
313	577.2585 (EI)	5-Amino-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide	Single stereoisomer; Prepared from amine of Preparation 137 (derived from Isomer 2 of Preparation 143)
314	550.2380 (FAB)	5-Amino-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide	Single stereoisomer; Derived from Isomer 1 of Preparation 147
315	550.2365 (FAB)	5-Amino-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide	Single stereoisomer; Derived from Isomer 2 of Preparation 147
316	596.2583 (FAB)	5-Amino-N-[3(R or S)-(1-[6(R or S)-(2-[4-fluorophenyl)ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethyl propyl)phenyl]-2-pyridine-sulfonamide	Single stereoisomer; Derived from Isomer 1 of Preparation 150
317	596.2583 (FAB)	5-Amino-N-[3(R or S)-(1-[6(R or S)-(2-[4-fluorophenyl]ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-2-pyridine-sulfonamide	Single stereoisomer; Derived from Isomer 2 of Preparation 150
318	503.2445 (EI)	N-[3(R or S)-(1-[5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-1-methyl-1H-imidazole-4-sulfonamide	Single enantiomer; Prepared from amine derived from Isomer 1 of Preparation 144
319	503.2454 (EI)	N-[3(R or S)-(1-[5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-1-methyl-1H-imidazole-4-sulfonamide	Single enantiomer; Prepared from amine derived from Isomer 2 of Preparation 144
320	515.2453 (EI)	5-Amino-N-[3(R or S)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethy-lpropyl)phenyl]-2-pyridine-sulfonamide	Single enantiomer; Prepared from amine derived from Isomer 1 of Preparation

TABLE 3-continued

U-No.	MS data	Name	Origin
			144
321	515.2463 (EI)	5-Amino-N-[3(R or S)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-2-pyridine-sulfonamide	Single enantiomer; Prepared from amine derived from Isomer 2 of Preparation 144
322	525.2287 (EI)	5-Cyano-N-[3(R or S)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-2-pyridine-sulfonamide	Single enantiomer; Prepared from amine derived from Isomer 2 of Preparation 144
323	525.2288 (EI)	5-Cyano-N-[3(R or S)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-2-pyridine-sulfonamide	Single enantiomer; Prepared from amine derived from Isomer 1 of Preparation 144
324	600.2537 (FAB)	N-[3(R or S)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide	Single enantiomer; Prepared from amine derived from Isomer 1 of Preparation 145
325	600.2537 (FAB)	N-[3(R or S)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide	Single enantiomer; Prepared from amine derived from Isomer 2 of Preparation 145
326	622.2378 (FAB)	N-[3(R or S)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide	Single enantiomer; Prepared from amine derived Isomer 1 of Preparation 145
327	622.2367 (FAB)	N-[3(R or S)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide	Single enantiomer; Prepared from amine derived from Isomer 2 of Preparation 145

We claim:

1. The compound of the formula VI



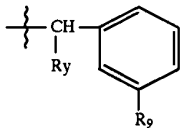
VI

wherein R_2 is

a) $H_3C—CH_2—$, or

b) phenyl-$(CH_2)_2$—;

wherein R_3 is the moiety of formula X



X

wherein R_6 is

a) $H_3C—(CH_2)_2$—, or

b) phenyl-$(CH_2)_2$—;

wherein R_7 is $H_3C—CH_2$—;

wherein R_9 is —$NHSO_2$—het;

wherein het is 2-pyridinyl substituted at the 5-position by zero (0) or one (1) R_{10};

wherein R_{10} is

a) —CN,

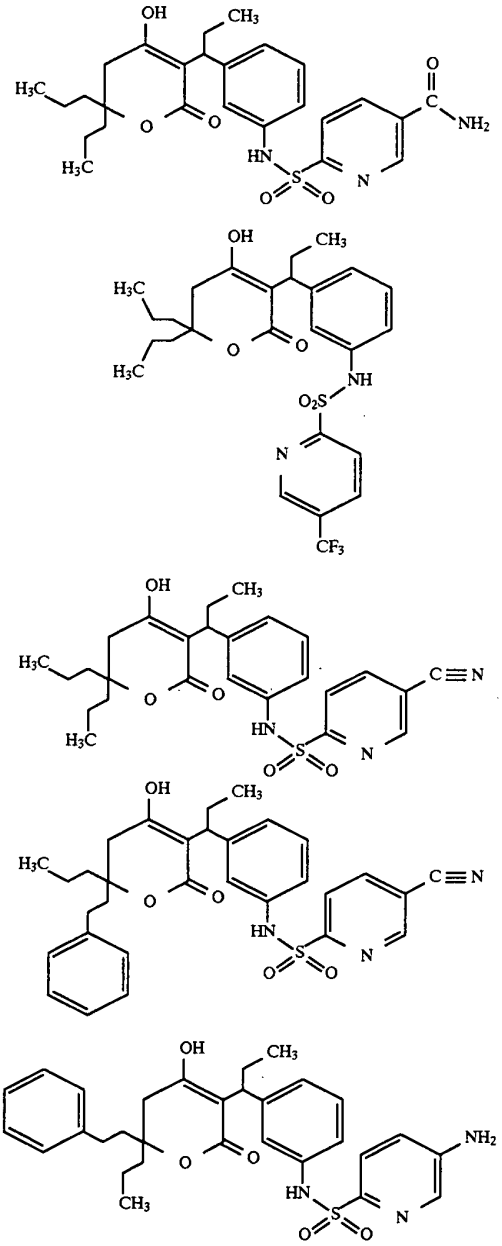
b) —CF_3,

c) —NH2, or

d) —$CONH_2$;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 selected from the group consisting of:



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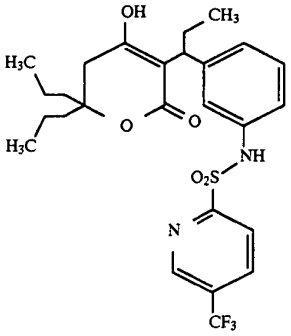

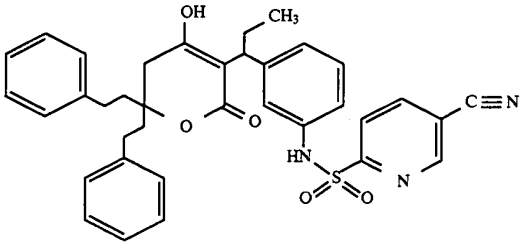

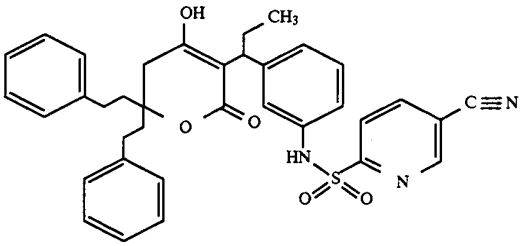

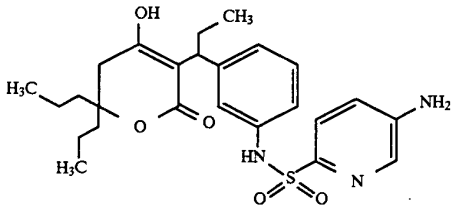

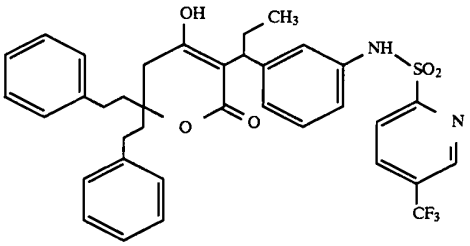

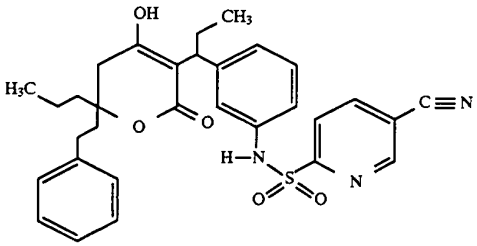

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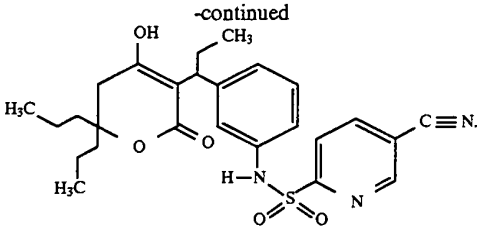


3. The compound of claim 1 selected from the group consisting of:

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide;

5-Trifluoromethyl-N-[3-(R)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide; or (3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl] phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

5-Trifluoromethyl-N-[3-(S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide; or (3S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl] phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridine sulfonamide;

5-Trifluoromethyl-N-[3(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6(R)-n-propyl-2H-pyran-3-yl] -propyl]-phenyl]-2-pyridinesulfonamide; or (3R,6R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl)propyl]-phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

5-Trifluoromethyl-N-[3(R)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6(S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide; or (3R,6S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl)propyl]-phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

5-Trifluoromethyl-N-[3(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R)-(2-phenethyl)-6(R)-n-propyl-2H-pyran-3-yl] -propyl]-phenyl]-2-pyridinesulfonamide; or (3S,6R)-N-[3-[1-[5,6,-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

5-Trifluoromethyl-N-[3(S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(S)-(2-phenethyl)-6(S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide; or (3S,6S)-N-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

N-[3-[1-(S)-[5,6,-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

(3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R or S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

N-[3-{1(R)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(R)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

N-[3-{1(S)-(4-Hydroxy-5,6-dihydro-2-oxo-6(S)-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

5-Amino-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl] propyl)phenyl]-2-pyridinesulfonamide;

5-Amino-N-[3(R or S)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl] propyl)phenyl]-2-pyridinesulfonamide;

5-Trifluoromethyl-N-[3-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide;

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

N-[3(R or S)-(1-[6,6-Bis(2-phenylethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide;

N-[3(R or S)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide;

N-[3-{1(R or S)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-aminopyridine-2-sulfonamide;

N-[3-{1(S or R)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-aminopyridine-2-sulfonamide;

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-phenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide;

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-phenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide;

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide;

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide; and

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl}phenyl]-5-carbamoylpyridine-2-sulfonamide.

4. The compound of claim **1** selected from the group consisting of:

(3R,6R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

(3R,6S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

(3S,6R)-N-[3-[1-[5,6,-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

(3S,6S)-N-[3-[1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide;

N-[3-[1-(S)-[5,6,-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide; and

(3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide.

5. A compound selected from the group consisting of:

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)methyl}phenyl]-5-cyanopyridine-2-sulfonamide, and

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)methyl}phenyl]-5-aminopyridine-2-sulfonamide.

* * * * *

EXHIBIT C
COPY OF CERTIFICATE OF CORRECTION
FOR U.S. PATENT 5,852,195

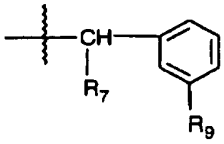
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,852,195
DATED : December 22, 1998
INVENTOR(S) : Romines, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 389,
Lines 60-65:



wherein R_6 is
a)$H_3C—(CH_2)_2—$, or

Signed and Sealed this

Ninth Day of October, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office

EXHIBIT D
COPY OF MAINTENANCE FEE RECORDS

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United States Patent and Trademark Office

Maintenance Fee Statement

07/08/2005 06:31 F

Patent Number: 5852195

Customer Number: 000000

MARTHA A. GAMMILL
INTELLECTUAL PROPERTY LEGAL SERVICES
PHARMACIA AND UPJOHN COMPANY
KALAMAZOO MI 49001

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If the statement of small entity status is defective the reason will be indicated below in the "Small Ent column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR-CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT
5,852,195	$880.00	$0.00	08/809,224	12/22/98	11/04/96	04	NO	PAID

Direct any questions about this notice to:
Mail Stop M Correspondence
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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Patent Maintenance Fees		07/08/2005 06:33 PM EDT	
Patent Number:	5852195	Application Number:	08809224
Issue Date:	12/22/1998	Filing Date:	11/04/1996
Window Opens:	12/22/2005	Surcharge Date:	06/23/2006
Window Closes:	12/22/2006	Payment Year:	
Entity Status:	LARGE		
Customer Number:	000000		
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City:	KALAMAZOO		
State:	MI		
Zip Code:	49001		
Phone Number:	(000) 000-0000		
Currently there are no fees due.			

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EXHIBIT E
INFORMATION TO ENABLE DETERMINATION
OF REGULATORY REVIEW PERIOD

Relevant Dates and Information to Enable
Determination of the Regulatory Review Period

The '195 patent claims a human drug product.

The Investigational New Drug (IND) application for the APTIVUS® product, IND No. 51979, was submitted on November 13, 1996, received by the FDA on November 14, 1996, and became effective 30 days after submission on December 13, 1996, pursuant to 21 C.F.R. §312.

The New Drug Application (NDA) for the APTIVUS® product, NDA No. 21-814, was submitted on December 21, 2004 and was approved by the FDA on June 22, 2005.

EXHIBIT F

DESCRIPTION OF SIGNIFICANT ACTIVITIES

This exhibit includes the following four chronolgies:

- Agency Contact Reports - Any phone calls, meetings or emails between BI and FDA
- Correspondence from FDA - Faxes or letters (hard copy) from FDA to BI
- IND Log - Listing of all submissions to the tipranavir IND 51,979
- NDA Log - Listing of all amendments to the tipranavir NDA 21-814 (NDA 21-822 (solution) cross references 21-814 for all clinical and non-clinical data)

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
11/21/96	FDA Letter Assigning IND Number	11/13/96	000	Original IND Application
12/17/96	FDA Fax providing clinical, pharmacology and microbiology comments on New IND and Protocol M/3342/001	11/13/96 12/13/96 12/13/96	000 N/A 001	Original IND Application PN&U and FDA Teleconference Protocol Amendment – Change in Protocol M/3342/0001
12/19/96	FDA Fax requesting information on drug substance, drug product and biopharmaceutics on New IND and Protocol M/3342/001	11/13/96 12/13/96 12/13/96	000 N/A 001	Original IND Application PN&U and FDA Teleconference Protocol Amendment – Change in Protocol M/3342/0001
1/27/97	FDA Letter providing clinical, pharmacology and microbiology comments on the IND and Protocol M/3342/001 Request for information regarding drug substance, drug product, and biopharmaceutics	12/13/96 12/17/96 12/19/96	N/A N/A N/A	PN&U and FDA Teleconference FDA Fax providing clinical, pharmacology and microbiology comments on New IND and Protocol M/3342/001 FDA Fax requesting information on drug substance, drug product and biopharmaceutics on New IND and Protocol M/3342/001
7/17/97	Letter informing PNU about the AIDS Clinical Trials Information Service (ACTIS) and requesting that PNU submits information about Protocol M/3342/0004 for the inclusion for the ACTIS database	1/2/97	003	Protocol Amendment – Change in Protocol M/3342/001 Amendment 2

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
2/27/98	FDA Fax providing biopharmaceutics comments on draft protocol M/3342/0009	2/4/98	018	Protocol Amendment – New Protocol Draft M/3342/0009
9/24/98	FDA Fax providing Biopharmaceutics comments on Protocol M/3342/0012	8/25/98	028	Protocol Amendment – New Protocol M/3342/0018
9/27/98	FDA Fax providing biopharmaceutics comments on Protocol M/3342/0009	2/4/98 2/27/98	018 018	Protocol Amendment – New Protocol Draft M/3342/0009 FDA Fax providing biopharmaceutics comments on draft protocol M/3342/0009
3/24/99	FDA Request for information – Clinical Comments on SN 040 and SN 041	1/29/99 2/5/99	040 041	Annual Report – Reporting Period 10/1/97 – 9/30-98 Protocol Amendment – New Protocol M3342/0006
4/21/99	Letter informing PNU about the AIDS Clinical Trials Information Service (ACTIS) and requesting that PNU submits information about Protocol M/3342/0006 for the inclusion for the ACTIS database	2/5/99 3/29/99	041 043	Protocol Amendment – New Protocol M/3342/0006 Protocol Amendment – • New Protocol M/3342/0013 • Change in Protocol M/3342/0006 Amendment 1
5/19/99	FDA Fax providing the FDA Meeting minutes from the May 11, 1999 Meeting discussing the Rat Carcinogenicity Study Dose Selection	5/11/99	N/A	FDA/PNU Meeting discussing the Rat Carcinogenicity Study Dose Selection

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
5/21/99	Letter informing PNU about the AIDS Clinical Trials Information Service (ACTIS) and requesting that PNU submits information about Protocol M/3342/0016 for the inclusion for the ACTIS database	5/10/99		Protocol Amendment – • New Protocol M/3342/0016
6/2/99	FDA Fax containing clinical comments on SN 049	5/10/99	049	• Protocol Amendment – • New Protocol M/3342/0016 • New Investigator for Protocol M/3342/0006 • New Investigator for Protocol M/3342/0013 • New Investigator for Protocol 69INF0013-019 • Change in Investigator for Protocol M/3342/0015
9/15/99	Letter encouraging all sponsors with antiretroviral drugs in development to conduct studies in treatment-exposed HIV-infected individuals and to promote pharmaceutical collaboration to meet this objective	N/A	N/A	N/A
5/15/00	Letter from FDA acknowledging transfer of IND from Pharmacia & Upjohn to Boehringer Ingelheim Pharmaceuticals effective April 21, 2000	4/19/00	068 069	General Correspondence – Transfer of Sponsorship from Pharmacia & Upjohn Company to Boehringer Ingelheim Pharmaceuticals, Inc. General Correspondence – Boehringer Ingelheim's acknowledgment of transfer of IND Sponsorship

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
9/13/00	Fax including FDA comments on Amendment 12 of Trial No. 1182.1	7/10/97 8/22/97 9/30/97 2/4/98 4/1/98 6/2/98 7/30/98 12/9/98 11/23/99 8/3/00	010 012 015 018 022 025 027 039 059 071	Original Protocol Amendment 1 Amendment 2 and 3 Amendment 4 and 5 Amendment A, 6 and 7 Amendment 8 Amendment 9 Amendment 10 Amendment 11 Amendment 12
11/9/00	Fax containing FDA comments on Protocol 1182.5	9/13/00	072	Protocol Amendment – New Protocol 1182.5
3/1/01	FDA fax providing clinical and pharmacokinetics comments on Protocol 1182.6	1/19/01	076	Protocol Amendment – New Protocol and New Investigator for 1182.6
3/5/01	FDA fax providing microbiological comment on Protocol 1182.6	1/19/01 3/1/01	076 076	Protocol Amendment – New Protocol and New Investigator for 1182.6 FDA fax providing clinical and pharmacokinetics comments on Protocol 1182.6

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
3/19/01	FDA Fax with clinical comments and requests for information regarding BI Trials	3/19/01	078	Protocol Amendment • New Protocol for 1182.17 • Change in Protocol 1182.4 Amendment 2 • Change in Protocol 1182.6 Amendment 1
6/29/01	Official FDA Meeting Minutes from the End of Phase I Meeting on April 5, 2001	4/5/01	077	End of Phase I Background Document
11/15/01	FDA Fax containing comments on SN 122	11/7/01	122	General Correspondence - Request for Advice on Duration of Combination Toxicology Studies
11/16/01	FDA Fax with clinical comments on BI Trial 1182.37 and 1182.41	11/16/01	121	Protocol Amendment • New Protocols 1182.37 and 1182.41 • Changes in Protocol 1182.37 Amendment 1
11/30/01	Official FDA Meeting Minutes from Clinical Development plans and drug interaction program for tipranavir on October 5, 2001	10/5/01 11/7/01	N/A 123	Meeting to discuss clinical development plans and drug interaction program BIPI's Meeting Minutes from 10/5/01 meeting
12/6/01	FDA Fax with clinical pharmacology comments on BI Trial 1182.41	11/16/01	121	Protocol Amendment • New Protocols 1182.37 and 1182.41
2/4/02	Fax from FDA requesting additional information in reference to SN 133	12/27/01	133	Response to FDA Comments in regards to combination toxicology studies

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
2/15/02	Fax from FDA Requesting Information from BI in order to address the clinical development program. FDA Requesting Chemistry, Pharmacology/Toxicology, Pharmacokinetics and Clinical information.	1/28/02 2/4/02 12/27/01	132 N/A 133	Information Amendment – Clinical Pharmacokinetics from 1182.6 Fax from FDA Requesting additional Information on SN 133 Response to FDA Comments in regards to combination toxicology studies
3/22/02	Letter encouraging all sponsors with antiretroviral drugs in development to conduct studies in treatment-exposed HIV-infected individuals and to promote pharmaceutical collaboration to meet this objective ACTIS database.	N/A	N/A	N/A
4/26/02	Letter encouraging all sponsors with antiretroviral drugs in development to conduct studies in treatment-exposed HIV-infected individuals and to promote pharmaceutical collaboration to meet this objective	N/A	N/A	N/A
5/17/02	Letter encouraging all sponsors with antiretroviral drugs in development to conduct studies in treatment-exposed HIV-infected individuals and to promote pharmaceutical collaboration to meet this objective	N/A	N/A	N/A

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
7/24/02	FDA Fax with Pharmacology comments on SN 162; FDA agrees with proposed change of dose level from 26.7 mg/kg/day for the ritonavir only arm of the rat carcinogenicity study protocol	7/19/02	162	• Information Amendment-Pharmacology/Toxicology Reports • Request for FDA Feedback/Teleconference – BI request concurrence with lowering dose level of ritonavir
8/29/02	Email from FDA with copy of FDA letter dated 8/29/02 acknowledging receipt of special clinical protocol assessment. FDA believes submission is not adequate for complete special protocol assessment because data is missing. FDA provides information that is required and refers to guidance for additional information.	7/18/02 6/7,6/18, 6/19 and 6/25/02	161 ACR	Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.52 Feedback on Special Protocol Assessment
8/29/02	FDA letter with acknowledging receipt of special clinical protocol assessment. FDA believes submission is not adequate for complete special protocol assessment because data is missing. FDA provides information that is required and refers to guidance for additional information.	7/18/02 8/29/02	161 161	Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.52 Email from FDA providing FDA Letter
9/20/02	FDA Fax providing clinical pharmacology comments on SN 137. FDA believes BI has not submitted sufficient information for the Division to conclude that further investigation of the drug interaction potential between ddI and tipranavir/ritonavir (TPV/RTV) is unnecessary. Reasons are provided.	2/14/02 12/20/01	137 132	Information Amendment: Clinical/Request for Comment-Discontinuation of Tipranavir Study 1182.42 Information Amendment - Clinical Pharmacokinetics from 1182.6

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
9/20/02	Fax from FDA with Comments on SN 161. FDA provides answers to the questions that were included in the Request for Special Protocol Assessment. Additional comments are also provided.	7/18/02	161	Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.52
10/3/02	Letter encouraging all sponsors with antiretroviral drugs in development to conduct studies in treatment-exposed HIV-infected individuals and to promote pharmaceutical collaboration to meet this objective	7/18/02	161	Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.52
10/30/02	FDA Fax with Overview of Pharmacology/Toxicology comments regarding the clinical development of tipranavir ? Human exposure ? Justification of Formulation (including info on vehicle	8/29/02	N/A	FDA letter with acknowledging receipt of special clinical protocol assessment. FDA believes submission is not adequate for complete special protocol assessment because data is missing. FDA provides information that is required and refers to guidance for additional information.
		7/18/02	161	Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.12
		9/20/02	N/A	Fax from FDA with Comments on SN 161. FDA provides answers to the questions that were included in the Request for Special Protocol Assessment. Additional comments are also provided.

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
		3/5/02- 5/17/02	139 150	Response to FDA Request - Providing information on the in-life data at 3 months from the ongoing six-month rat and dog toxicology studies, the oral toxicity of polyoxy135 castor oil in animals and SEDDS formulations used for other drugs in preclinical/clinical trials
12/10/02	Fax from FDA with Clinical and Clinical Pharmacology comments regarding SN 186. FDA Requests that responses are provided prior to the End of Phase II Meeting	11/15/02	186	General Correspondence - Background Document for End of Phase II Meeting
12/12/02	FDA Fax with Pharmacology/Toxicology comments in preparation for the December 12, 2002 teleconference	12/4/02	N/A	Teleconference between BI and FDA
12/31/02	FDA Fax providing Clinical and Statistical comments regarding Protocol 1182.12	11/15/02 12/17/02	186 N/A	General Correspondence - Background Document for End of Phase II Meeting End of Phase II Meeting

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
1/3/03	FDA Fax with Microbiology comments regarding SN 186	11/15/02	186	General Correspondence - Background Document for End of Phase II Meeting
		12/17/02	N/A	End of Phase II Meeting
1/14/03	FDA Official Meeting Minutes from the End of Phase II Meeting	12/17/02	N/A	End of Phase II Meeting
		3/14/03	N/A	FDA End of Phase II Meeting Minutes
		3/24/03	217	BIPI End of Phase II Meeting Minutes
1/22/03	FDA Letter requesting additional information on pediatric studies. BI must submit the requested information with clearly marked submissions within 180 days.	11/15/02	186	General Correspondence - Background Document for End of Phase II Meeting
		3/14/03	N/A	FDA End of Phase II Meeting Minutes
		3/24/03	217	BIPI End of Phase II Meeting Minutes
4/14/03	FDA's response to New Protocol 1182.51	1/30/03	204	Protocol Amendment – New Protocol 1182.51
5/7/03	FDA Fax providing Response to Carcinogenicity Special Protocol Assessment Report – Final CAC Report. FDA recommends BI to evaluate the dosage groups by pair wise comparison with the negative control.	3/24/03	216	Request for Special Protocol Assessment – Carcinogenicity Study Protocol. BI asking FDA concurrence with the mouse carcinogenicity study protocol.
		6/7/02 6/18/02 6/19/02 6/25/02	ACRS	Special Protocol Assessment for mouse carcinogenicity protocol.
5/30/03	FDA Approval to export tipranavir to Brazil for 1182.48	5/12/03	N/A	Request to Export Drug to Brazil for 1182.48
		5/8/03	ACR	DAVDP's review of export waiver
		4/8/03 -	ACR	Export waiver status

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
		11/03		
5/30/03	FDA Approval to export tipranavir to Argentina for 1182.48	3/12/04 4/8/03-11/03	N/A ACR	Request to Export Drug to Argentina for 1182.48 Export waiver status
5/30/03	FDA Approval to export tipranavir to Mexico for 1182.48	3/14/04	N/A	Request to Export Drug to Mexico for 1182.48
9/4/03	Response to BI's request for a teleconference to discuss proposed pediatric written agreement. FDA classified the meeting as Type B and it is scheduled for September 18, 2003	7/23/03 8/26/03 8/15/03 1/22/03 & 1/28/03	242 ACR ACR N/A	Proposed Changes in Written Request for Pediatric Studies Proposed date of telecom Request for telecon Proposed Written Agreement for Pediatric Studies
9/15/03	FDA Approval to export tipranavir to Brazil for 1182.17	7/23/03	N/A	Request to Export Drug to Brazil for 1182.17
9/16/03	FDA Fax providing statistical comments on Protocol 1182.12 (RESIST 1)	3/19/03 2/4/03	SN 214 SN 205	Protocol Amendment – Changes in Protocol 1182.12 Amendment 1 and 2 Original Protocol

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
9/17/03	FDA Approval to export tipranavir to Argentina for 1182.17	7/23/03	N/A	Request to Export drug to Argentina for 1182.17
		6/6/03	ACR	
		9/6/03-9/8/03	ACR	Export waiver – 1182.17 for Argentina
		8/23/03-8/29/03	ACR	Request for status of export waiver
		8/6/03-8/8/03	ACR	Request for status of export waiver
		8/12/03-8/15/03	ACR	Request for status of export waiver
		7/31/03-8/15/03	ACR	Request for status of export waiver
9/25/03	FDA Fax containing Comments regarding responses to proposed written agreement for pediatric studies	7/23/03	242	Proposed Changes in Written Request for Pediatric Studies Proposed Written Agreement for Pediatric Studies Request for Teleconference to discuss submission
10/31/03	FDA Official Meeting Minutes from the teleconference discussing the Proposed Changes in Written Request for Pediatric Studies	10/2/03	N/A	BI and FDA Teleconference discussing the Proposed Changes in Written Request for Pediatric Studies
		7/23/03	186	Proposed Changes in Written Request for Pediatric Studies

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
11/13/03	FDA Letter with Responses to Request for Special Protocol Assessment – Clinical, Naïve Trial 1182.33	9/26/03	254	Request for Special Protocol Assessment – Clinical, Naïve Trial 1182.33
		10/24/03	ACR	Naïve Trial 1182.33
		7/18/03	ACR	Naïve Trial 1182.33
		7/15/03	ACR	Naïve Trial 1182.33
		12/17/02	N/A	End of Phase II Meeting
11/13/03	FDA Acknowledgment of Receipt of Request for Special Protocol Assessment – Clinical, Naïve Trial 1182.33	9/26/03	254	Request for Special Protocol Assessment – Clinical, Naïve Trial 1182.33
11/14/03	FDA Approval to export tipranavir to Brazil for 1182.14	8/20/03	N/A	Request to Export Drug to Brazil for 1182.14
11/14/03	FDA Approval to export tipranavir to Argentina for 1182.14	8/20/03	N/A	Request to Export Drug to Argentina for 1182.14
11/14/03	FDA Approval to export tipranavir to Mexico for 1182.14	8/20/03	N/A	Request to Export Drug to Mexico for 1182.14
11/14/03	FDA Approval to export tipranavir to Russia for 1182.14	9/8/03	N/A	Request to Export Drug to Russia for 1182.14

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
12/12/03	FDA Approval to export tipranavir to Russia, Brazil, Argentina and Mexico for 1182.14	9/8/03 8/20/03 8/20/03 8/20/03	N/A N/A N/A N/A	Request to Export Drug to Russia for 1182.14 Request to Export Drug to Brazil for 1182.14 Request to Export Drug to Argentina for 1182.14 Request to Export Drug to Mexico for 1182.14
2/20/04	Letter from FDA confirming with BI that a Type B Meeting is scheduled for May 10, 2004.	1/30/04	297	General Correspondence – Request for Pre-NDA Meeting
3/3/04	FDA Official Meeting Minutes from the Meeting discussing BI's safety reporting policies and procedures	1/16/04	N/A	Meeting discussing BI's safety reporting procedures and policies
3/12/04	FDA Fax regarding Quality of Life analyses in RESIST 1 study	1/5/04	276	Information Amendment – Clinical Request for FDA Comments on Special Protocol Assessment for Protocol 1182.12 (RESIST 1)
4/16/04	FDA Fax regarding CMC comments regarding upcoming meeting	3/19/04 4/13/04	349 381	Info Package for Type B Pre-NDA Mtg. Amendment to Info Package for Type B Pre-NDA Mtg.
5/18/04	FDA Fax regarding Pharmacology/Toxicology Comments SN 318	2/20/04	318	Request for FDA Feedback on BI plans for immunotoxicology testing
6/3/04	FDA Fax regarding DSI request for investigator and study site information for inspections	12/21/04	21-814	Original NDA
6/8/04	FDA Fax – List of Attendees from June 2, 2004 face-to-face pre-NDA meeting for Tipranavir (IND 51,979)	7/19/04	SN 520	Pre-NDA meeting Minutes

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
6/22/04	FDA Fax – CMC questions for TPV Oral Solution face-to-face meeting – June 24, 2004	6/11/04	SN 460	Information Amendment CMC Type A IND Meeting Information Package for Oral Sol.
7/2/04	FDA Fax – Pharmacology/Toxicology comment reqarding SN 470	6/17/04	470	Information Amendment: PharmTox 24-month oral Rat Carcinogenicity Study – Request for FDA Feedback on planned termination of study arm due to mortality rates.
8/12/04	FDA Fax – Microbiology Comments for IND 51,979 SN 534	7/28/04	534	Request for FDA Feedback - Proposal for in vitro study of ARV's
8/12/04	FDA Fax – Microbiology Comments for IND 51,979 SN 527	7/22/04	527	Information Amendment: Pharmacology/Toxicology –(U03-3565, U03-3153)
8/30/04	FDA Letter – PRE-NDA CMC Meeting (type B) meeting minutes – April 19, 2004	4/19/04 3/19/04	N/A 314	Pre-NDA Meeting Pre-NDA Background Document
10/08/04	FDA Fax – DDMAC comments regarding the press release for treatment IND 70,629 for TPV expanded access program	9/30/04	SN002	Submission of Press Release
10/08/04	FDA Fax – Treatment IND 70,629 TPV expanded access program	9/7/04	N/A	Original Treatment IND 70,629
10/20/04	FDA Fax – Clinical Request for Pre-submission data - # of deaths for NDA 21-814	N/A	N/A	N/A
10/25/04	FDA Fax – Clinical and Clinical Pharmacology comments for IND 51,979, SN 577	9/10/04	577	Protocol Amendment: Final Draft Protocol 1182.60 (QT Prolongation Study)
11/5/04	FDA Fax – Clinical Comments for latest IB IND 51,979, SN 594	11/1/04	594	Investigators Brochure – Version 8

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
11/12/04	FDA Fax – Clinical Request for NDA 21-814 for TPV. CRT datasets difficult to review, requested modification of datasets to facilitate review	12/21/04	21-814	Original NDA
11/12/04	FDA Letter- Official minutes – Pre-NDA meeting June 2, 2004	6/2/2004 7/19/01	N/A 521	Pre-NDA Meeting BI's Pre-NDA Meeting Minutes
11/15/04	FDA Letter – Acknowledge receipt of NDA (21814, 21822)	12/21/04 12/21/04	21-814 21-822	Original NDA – Capsules Original NDA – Solution
11/23/04	Email: Clinical Comments in regards to meeting held on November 22, 2004	11/22/04	N/A	FDA Meeting
11/24/04	Email: Statistics Request	12/21/04	N/A	Original NDA
11/30/04	Email: Questions for Medical/Statistics Reviewers	12/21/04	21-814	Original NDA
12/01/04	Email: TPV Request re: Microbiology	12/21/04	21-814	Original NDA
12/02/04	Email: TPV query 12/2/04 re 1182.12 Study report	12/21/04	21-814	Original NDA
12/02/04	Email: Questions from Medical/Statistics Reviewers	11/30/04	N/A	N/A
12/17/04	FDA Letter – Official Telecon minutes - withdraw of NDA	12/21/04 12/17/04	21-814 N/A	Original NDA Telecon
12/21/04	FDA Fax – Acknowledge receipt of BIPI correspondence notifying FDA of withdrawal of NDA's	12/21/04 12/20/04	21-814, 21-822	Original NDA's Withdrawal of NDA's
2/8/05	FDA FAX – Tentative Date for TPV Advisory Committee Meeting	N/A	N/A	N/A
2/20/05	FDA Fax – Letter informing of upcoming FDA advisory committee meeting	N/A	N/A	N/A

TIPRANAVIR CORRESPONDENCE FROM FDA

Date of FDA Correspondence	Description of FDA Correspondence	Date of Reference	Serial Number of Reference	Description of Reference
3/4/05	FDA Acknowledgement of Receipt of 12/20/04 Withdrawal and 12/21/04 Resubmission. FDA will give Priority Review.	N/A	N/A	.N/A
3/7/05	FDA FAX – TPV 74 day filing letter	12/21/04	21-814	Original NDA
3/24/05	FDA FAX – Pharm/Tox comments for NDA 21-814 for TPV- Comments on behalf of Dr. Bigger	12/21/04	21-814	Original NDA
4/22/05	ACR - FDA Background Document for upcoming 5/19/05 Advisory Committee Meeting.	N/A	N/A	N/A
5/5/05	FDA fax – Agency backgrounder Background document provided by CDER to the Advisory Committee Members for the upcoming 5/19/05 meeting	N/A	N/A	N/A
6/22/05	NDA Approval Letter	12/21/04	21-814	Original NDA
6/23/05	FDA letter stating that labeling attached to the approval letter was incorrect	6/22/05	21-814	NDA Approval Letter

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
001	10/27/04	• Response to FDA Request for Information – deaths from studies .12, .48, .17,.1, .4, .5, .51, .52, and .58 along with all 7day faxes of deaths and narratives for each death	FDA Fax	10/20/04	Response to FDA Fax dated October 20, 2004 requesting info on TPV deaths in studies 1182.12, 1182.48, 1182.17 and 1182.58
002	10/29/04	• Replacement Volume – Module 2 Volume 1.6 – Summary of Clinical Safety	A001	10/21/04	Safety (replacement volume to correct technical error in cross referencing of original 1.6 submitted in original NDA dated October 21, 2004.
003	11/01/04	• Electronic Submission Update:Corporate Drug Safety Dataset	Original NDA A001	10/21/04 10/27/04	Original dataset included in October 21, 2004 Original NDA Updated electronic dataset to include info in Amendment 1
004	11/03/04	• General Correspondence / Request for FDA Feedback: Proposal for 2 Month Safety Update	Pre-NDAMeeting SN 521	6/2/04 7/15/04	At meeting BI discussed the request for priority review and in preparation, BI will submit proposal for 2 Month Safety Update Pre-NDA Meeting Minutes

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
005	11/12/04	• Response to FDA Request for Information: Updated Information on Tipranavir Deaths	A001 E-mail	10/27/04 11/05/04	Per e-mail request from Ms. Tanima Sinha dated November 5, 2004, requesting additional information for Dr. Andrea James in reference to Amendment 1
006	11/17/04	• Response to FDA Request for Information: Updated Information on Tipranavir Datasets	FDA Fax	11/12/04	Fax request of Ms. Sinha dated November 12, 2004 per Clinical reviewers' having difficulty reviewing some of the datasets
007	11/18/04	• General Correspondence / Request for Feedback: Agenda Topics to be discussed on the requested meeting	Agency Contact	11/17/04	Per telephone discussion with Ms. Tanima Sinha dated November 17, 2004, requesting a meeting with BI on November 22, 2004, summary of understanding of issues identified with NDA submission.
008	11/30/04	• General Correspondence: Justification for Priority Review	Telecon	11/24/04	Telecon with FDA 11/24/04: Agreement made that BIPI would submit a short justification for priority Review.
009	12/03/04	• General Correspondence: Proposed Electronic Submission Timeline	FDA Meeting Telecon Agency	11/22/04 11/23/04 12/03/04	As agreed during telephone discussion with Drs. Blank and Kaplan, and per discussion with Ms. Sinha, BI is providing a description of all action items agreed between the Division and BI at the meeting

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
			Contact		of November 22 and in communication since that time.
010	12/03/04	• Response to FDA Request for Information: Updated Resistance Dataset	e-mail	12/01/04	Microbiology Reviewers', Kimberly Struble and Lisa Naeger, comments regarding the Tipranavir BASE-RES Dataset.
011	12/05/04	• Response to FDA Request for Information – Updated Information of TPV Datasets: Response to Requests from Nov 22, 2004 meeting	Telefax FDA Meeting	11/12/04 11/22/04	Facsimile request from ms. Tanima Sinha, dated November 12, 2004 with Reviewers' comments regarding the CRT datasets.
012	12/06/04	• Response to FDA Request for Information – Comments regarding 1182.12 study report	e-mail	12/02/04	E-mail request from Ms. Tanima Sinha dated December 2, 2004, on behalf of clinical Reviewer, Dr. James with comments regarding the 1182.12 study report

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
013	12/06/04	• Response to FDA Request for Information – Proposals to items 5, 8 and 9 from our BDM group. Example of SAS dataset	FDA Meeting E-mail Amend 011	11/22/04 11/23/04 12/05/04	E-mail request from Ms. Tanima Sinha dated November 23, 2004, with Reviewers' comments summarized from our November 22, 2004 meeting
014	12/09/04	• Response to FDA Request for Information: Updated Information on Tipranavir Datasets – Final changes from FDA meeting on Nov. 22, 2004 + side requests	FDA Meeting E-mail A 011 Telecon	11/22/04 11/23/04 12/05/04 12/07/04	E-mail request from Ms. Tanima Sinha dated November 23, 2004, with Reviewers' comments summarized from our November 22, 2004 meeting. Reference also made to a teleconference held on Dec ember 7, 2004.
015	12/17/04	• Response to FDA Request for Information – PK reviewer Questions of November 24, 2004 and December 3, 2004	E-mail	11/24/04	E-mail request from Ms. Tanima Sinha on behalf of PK reviewer dated November 24, 2004 and December 23, 2004.
N/A	12/20/04	Request to withdraw New Drug Application	Original NDA	10/21/04	Original New Drug Application
N/A	12/21/04	Resubmission of New Drug Application	Original NDA Withdrawal of NDA	10/21/04 12/20/04	Original New Drug Application Withdrawal of New Drug Application
016	12/29/04	• Response to Request for	Telecon	12/20/04	Dr. James requested that BI submit a new

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
		Information - Replacement E-Submission	E-mail	12/20/04	electronic submission with all updated datasets submitted since October 22, 2004
017	1/4/05	• Response to FDA Request for Information – Immunotoxicity Study	SN 381 Telecon E-mail	2/20/04 8/30/04 9/17/04	BI immunotox proposal BI agreed to conduct study Summary of Immunotoxicity Study 04R103 would be available for Jan. 4, 2004
018	1/12/05	• Response to FDA Request for Information – Statistical – RESIST 1 and 2	E-mail	1/7/05	Statistical comments/questions refer to data for RESIST 1 (Study 1182.12) and RESIST 2 (Study 1182.48)
019	1/13/05	• Response to FDA Request for Information - Statistical request for cutoff dates/ patient exposures for e-datasests	E-mail	1/11/05	Email request from FDA Requesting a table showing the database lock dates and length of follow-up of patients for each electronic data submission to the NDA

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
020	1/25/05	• Response to FDA Request for Information - In Vitro Virologic Interations Study	Pre-NDA Mtg	6/2/04	N/A
			SN 534	7/28/04	BI submission requesting feedback on the study design and timing, response to request of SN 534
			E-mail	8/12/04	Request for info on in-vitro virologic interactions study
021	1/25/05	• General Correspondence: December 17, 2004 Meeting Minutes / Request for Change to Official FDA Meeting Minutes	Meeting	12/17/04	Meeting between BIPI and Division
22	2/2/05	• Written Responses to November 17, 2004 e-mail.	E-mail	11/17/04	Request from stat reviewer, Dr. Bhore with comments regarding the CRT datasets.
23	2/3/05	• Background Therapy Optimization Tablets	E-mail	1/31/05	Request from Dr. Liang in preparation for teleconference February 4, 2005. request for tables reformatting data for patients in Resist 1 and Resist 2.

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
24	2/9/05	• Rheumatology or Dermatology consults for Trial 1182.22	Email	2/3/05	FDA Requesting pictures electronically for section 16.4 of Report 1182.22
25	2/10/05	• Response to FDA Optimization and Listings of 1182.12 and 1182.48 RESIST Studies (datasets)	FDA Letter and Telecon	1/31/05, 2/4/05	FDA questioning background therapy optimzation
26	2/10/05	• Response to FDA request regarding RESIST 1 and RESIST 2 discontinuations	Email	2/8/05	Email Request from Dr. Bhore and Dr. Baylor – requesting RESIST 1 and RESIST 2 discontinuations
27	2/16/06	• Response to Request for Information - Resubmission of Rheumatology and Dermatology Consults –	Email	2/3/05	FDA Requesting pictures electronically for section 16.4 of Report 1182.22
28	2/16/05	• Response to FDA Request for Information: Updated Information on Tipranavir Datasets	Email	2/2/05	Request from Ms. Monica Zeballos with Clinical, Statistical and PK queries.
29	2/22/05	• 2 Month Safety Update Report	A004 Telecon	11/3/04 12/17/04	Requesting FDA feedback on 2MSUR FDA agreed to the proposal and timing for the submission of the 2MSUR

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
30	2/23/05	• Response to Request for Information - Resistance Datasets	Meetings	6/4/04, 10/4/04	Pre-NDA Meeting Electronic submission demonstration
31	2/25/05	• Response to Request for Information on trials 1182.4, 1182.6, 1182.51 & 1182.22	Email	2/14/05	Query from Dr. Gibbs regarding trials 1182.4, 1182.6, 1182.51 and 1182.22
32	2/28/05	• Response to Request for Information on Datasets	Email	2/25/05	FDA query (Dr. Bhore) regarding Resist I clinical trials (Studies 1182.12 and 1182.48)
33	2/28/05	• Response to Request for Information – updated ARV datasets for trials 1182.51 and 1182.52	E-mail	2/18/05	Updated ARV datasets for trials 1182.51 and 1182.52
34	3/3/05	• Response to FDA Request for	Telecon	8/30/04	Discussion of immunotoxicity program

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
		information – Final Immunotoxicity Report U05-3021	SN 318 SN 582 A017	2/20/04 9/23/04 3/3/05	Submission describing program Requesting feedback on the adequacy of the protocol design Summary of study 04R013 (U05-3021).
35	3/4/05	• Response to FDA Request for information. CRF's for 1182.12 subjects.	E-mail	3/1/05	E-mail request of March 1, 2005 from Clinical Reviewer, Dr. James with a request for case report forms for subjects in the 1182.12 trial.
36	3/15/05	• Response to FDA Request for Information Additional CRF's for 2MSUR	A028 Telecon NDA filing	2/22/05 3/9/05 3/10/05	2 Month Safety Update Report N/A NDA Filing communication
37	3/15/05	• Response to FDA Request for Information;Adverse Event Information for Naïve Study	E-mail	3/10/05	Ms. Tanima Sinha of behalf of Dr. Melisse Baylor requesting information for the Naïve Study (1182.33)

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
		1182.33			
38	3/15/05	• Response to FDA Request:- country De-codes	E-mail	3/14/05	Ms. Tanima Sinha on behalf from Dr. Bhore regarding country codes.
39	3/16/05	Response to FDA Request of March 9, 2005: micro reviewer queries	E-mail	3/9/05	Ms. Tanima Sinha on behalf of Dr. Naeger – comments and clarifications requested for report U00-3184.
40	3/17/05	• Response to FDA Request for Information;Request of March 10, 2005 statistical queries.	E-mail	3/10/05	Comments and queries regarding Resist I clinical trials 1182.12 and 882.48.
41	3/21/05	• CMC Amendment – updated stability - Change in Proposed Storage Conditions	N/A	N/A	N/A
42	3/24/05	• Response to FDA Request for Information:Laboratory Information for Naïve Study.	E-mail A037	3/10/05 3/15/05	e-mail request from Ms. Tanima Sinha on behalf of Dr,. Baylor Adverse Event information for Naïve study
43	3/24/05	• Advisory committee meeting package – DRAFT background document for 4/4/05 meeting	Telecon	3/21/05	Discussed proposed agenda for ADVAC meeting.

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
44	3/24/05	CMC Amendment - Additional data to justify the specification for an additional excipient	N/A	N/A	N/A
45	3/25/05	Labeling Update and Resistance Amendment -Tipranavir Analysis of Emergent Resistance/Revised Labeling	A029 A030	2/22//05 2/23/05	2 Month Safety Update Response to Request for Information - Resistance Datasets
46	3/31/05	Response to FDA Request for Information Dog Bioavailability Study	A044 E-mail	3/24/05 3/30/05	CMC Amendment justifying additional excipient Pharmacology Toxicology Query on Amendment 044
47	3/31/05	• Response to FDA Request for Information – Microbiology – phenotypic data	E-mail & Telecon	3/23/05	Micro Requests from Lisa Naeger on phenotypic data.
48	4/4/2005	Revised Labeling – revised labeling reflecting pk responses	Telecon	3/16/05	PK request – revised labeling

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
49	4/6/05	Response to FDA Request for Info Protocol Deviations – Resist 1 & 2	E-mail	3/10/05	On behalf of stat reviewer, Dr. James with relevant protocol deviation queries for RESIST 1 and 2 studies
50	4/7/05	Response to FDA Request for Information – Data Coding	Agency Contact Telecon	3/14/05 3/16/05	Statistical queries regarding data coding Telecon on Statistical queries regarding data coding
51	4/11/05	Response to FDA Request for Information – AIDS defining event	E-mail	4/7/05	Tanima Sinha's e-mail dated April 7, 2005, regarding the new AIDS defining event.
52	4/12/05	Response to FDA Request for Information – statistical queries	E-mail	4/8/05	statistical queries
53	4/12/05	Request for FDA Feedback on Resistance Section of AVDAC Briefing document	Telecon	4/11/05	Teleconference regarding the Resistance Section of the AVDAC Briefing Document
54	4/15/05	Response to FDA Request for Information – lab data information	E-mail	3/28/05	Request asking for lab data information
55	4/15/05	Response to FDA Request for Information – genotype sensitivity score in RESIST trials.	E-mail	4/14/05	Statistics query regarding the genotype sensitivity score (GSS) in RESIST trials

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
56	4/15/05	Revised Labeling Table 1 (Drug Interactions) Correction to Amendment 048	A048	4/1/05	Revised labeling submitted April 1, 2005, correction to table 1
57	4/19/05	General Correspondence: Tipranavir Advisory Committee Briefing Document	Telecon A053	4/11/05 4/12/05	Teleconference regarding the Resistance Section of the AVDAC Briefing Document Request for FDA Feedback on Resistance Section of AVDAC Briefing Document
58	4/19/05	Response to FDA Request for Information – efficacy analysis from the RESIST program	E-mail Telecon	4/13/05 4/14/05	Dr. Bhore's tipranavir efficacy analysis from the RESIST program Discussed potential reasons for differences in the outcome of Dr. Bhores analysis versus BIPI's.
59	4/19/05	Response to FDA Request for Information – patient disposition	E-mail	4/7/05	Statistical queries from Dr. Bhore on patient disposition

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
60	4/19/05	Response to FDA Request for Information – protocol deviation datasets	A49 Telephone Discussion/e-mail	4/6/05 4/18/05	Reference Amendment 49 on April 6, 2005 and telephone discussion as well as email on April 18, 2005 asking for new protocol deviation datasets
61	4/21/05	Response to FDA Request 74 Day Filing Letter	Letter	3/7/05	Reference to 74 Day Filing Letter from March 7, 2005
62	4/28/05	Response to FDA Request for Information – OBR Definition	E-mail	4/27/05	Statistical Query – OBR Definition
63	4/29/05	Response to FDA Request for Information – datasets on protocol violations	E-mail	4/29/05	Dr. Andrea James' request that BI direct her to the raw or analysis datasets that will provide information on protocol violations
64	4/29/05	Response to FDA Request for Information – location of tables for the classification of toxicity grading for studies .4, .12, .48, .51 and .52	E-mail	4/29/05	On behalf of Medical reviewer requesting the location of tables for the classification of toxicity grading for studies 1182.4, .12, .48, .51, and .52.
65	5/2/05	Background Documentation for May	A057	4/19/05	TPV Advisory Committee Briefing

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
		4, 2005 Teleconference AVDAC Presentation slides	Telecon	4/27/05	Document Current version of AVDAC presentation
66	5/5/05	Response to FDA Request for Information- specific resist patient lab and AES and patient disposition	E-mail	4/29/05	Query from Dr. James regarding specific individual resist patient lab and clinical, AES and patient disposition
67	5/10/05	Response to FDA Request for Information – lipodystrophy data	E-mail	5/10/05	Query from Dr. James regarding data for lipodystrophy
68	5/10/05	Background Information for May 11, 2004 telecon – updated slides for resistance presentation	A057 A065	4/19/05 5/2/05	TPV Advisory Committee Briefing Document Background Document for AVDAC
69	5/11/05	Response to FDA Request for Information – In vitro activity assessments	E-mail	4/4/05	Request for In vitro combination activity assessments
70	5/13/05	Response to FDA Request for Information – response to efficacy analysis for RESIST 1 and RESIST 2	E-mail Telecon	4/13/05 4/14/05	Dr. Bhore's tipranvir efficacy analysis from the RESIST program Discussed potential reasons for differences

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
					in the outcome of Dr. Bhores analysis versus BIPI's
			A058	4/19/05	Response to FDA Request for Information – efficacy analysis from the RESIST program
			E-mail	5/4/05	E-mail query on behalf of Dr. Bhore regarding efficacy analyses of RESIST 1 and RESIST 2
71	5/13/05	Response to FDA Request for Information – Sample of letter to Investigators re: Drug Metabolism and Interaction	E-mail	3/16/05	Expanded access program Investigators Brochure –EAP Investigators brochure – FDA requests BIPI inform investigators of information on Drug Metabolism and Interaction.
			telecon	4/27/05 &5/24/05	BIPI agreement to inform investigators

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
72	5/16/05	General Correspondence - Additional Slides for ADVAC	A057	4/19/05	ADVAC Briefing Document
			N/A	4/22/05	FDA's ADVAC Briefing Document
			Telecon	4/27/05	Current version of ADVAC presentation
			A065	5/2/05	Background Documentation for May 4, 2005 Teleconference ADVAC Presentation Slides
			Telecon	5/11/05	Informing FDA BIPI will submit additional slides for ADVAC meeting
73	5/24/05	Response to FDA Request for Information – response to Pharm, Tox and CMC questions of 5/13/05	Telefax	5/13/05	FDA Questions, Pharmacology/Toxicology/CMC
74	5/27/05	Response to FDA Request for Information – Response to CMC questions of 5/13/05	Telefax	5/13/05	CMC Questions
75	6/3/05	Response to FDA Request – Revised Labeling	Telecon	6/8/05	Revised labeling to support the scheduled teleconference between the Division and BI on June 8, 2005.

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
76	6/07/05	General Correspondence – Post Marketing Commitments – Clinical and Toxicology	Telecon	6/1/05	Ms. Tanima Sinha requested that BI provide a proposal for post-marketing commitments
77	6/10/05	CMC – Amendment to a Pending Application – Updated specifications for drug substance, per FDA comments.	E-mail	6/7/05	FDA comments on the specifications for tipranavir drug substance and capsules.
78	6/10/05	Response to FDA Information Request - Environmental Analysis query of 6/7/05	E-mail	6/7/05	FDA's Information Request regarding Environmental Analysis.
79	6/17/05	CMC – Amendment to a Pending Application: Updated specification for drug product dissolution per FDA and BIPI agreement.	A077	6/10/05	BI agreement to FDA's proposed acceptance criterion for drug product specification and drug product dissolution
80	6/21/05	Post marketing commitments	Telecon	6/1/05	FDA request for post-marketing commitments proposal

Tipranavir Capsules NDA 21-814 Submission Log

Amendment	Date of Submission	Description of Submission	Reference	Date of Reference	Description of Reference
81	6/21/05	General Correspondence – Revised Labeling which incorporates all changes agreed to by members Division and BIPI to date.	A075 Telecon/E-mail	6/3/05 Multiple	Labeling Revision Multiple communications via teleconference and e-mail since 6/3/05 submission.

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
6/22/05	Amended Approval Letter, Capsules	Ms. Tanima Sinha Project Manager	NA	NA	NA
6/22/05	Final capsule approval letter	Ms. Tanima Sinha Project Manager	NA	NA	NA
6/22/05	Final medical reviewer query; final review of bottle label; final label revisions	Ms. Tanima Sinha Project Manager	NA	NA	NA
6/16/05	FDA comments from DSRCS regarding the PPI for TPV	Ms. Tanima Sinha Project Manager	NA	NA	NA
6/10/05	Status of Clin Stat commentsfor upcoming CMC telecom on 6/10/05 CMC telecon	Ms. Tanima Sinha Project Manager	NA	NA	NA
6/10/05	Final Report of Immunotoxicity Study	Ms. Tanima Sinha Project Manager	1/4/05	606	IA/Pharmacology/Toxicology Study summary of unaudited draft res
6/1/05	Request for Revised Labeling Request for post-marketing commitments proposal	Ms. Tanima Sinha Project Manager	NA	NA	NA

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
5/19/05	AVDAC	DAVDP, AVDAC	4/19/05	A057	Response to FDA Request for Information – Draft Advisory Committee Briefing document
			5/2/05	A065	AVDAC slides
			4/22/05	NA	FDA AVDAC Briefing Document
			Multiple	ACR	Meetings, telecons, to address Upcoming AVDAC
5/11/05	FDA stat response on primary efficacy results of the resist trials/amendment 058 for telecon – 11 May 2005	Ms. Tanima Sinha Project Manager	4/19/05	A057	Response to FDA Request for Information – Draft Advisory Committee Briefing document:
5/10/05	Final BI presentation team and order of presentations for ADVAC meeting	Ms. Anuja Patel, MPH Health Science Administrator	4/19/05	A057	General Correspondence:TPV Advisory Committee Meeting Briefing document (DRAFT)

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
5/10/05	FDA query on Lipodystrophy information in datasets from Dr. James	Ms. Tanima Sinha Project Manager	NA	NA	NA
5/3/05	FDA request to reschedule telecon to 6 May 2005 at 9:00am	Elizabeth Thompson Project Manager, DAVDP	N/A	N/A	N/A
5/2/05	Request for FDA feedback on BI AVDAC presentation/Request for copy of FDA's AVDAC presentation	Ms. Tanima Sinha Project Manager	4/19/05	057	General Correspondence: Advisory Committee Briefing Document - DRAFT
4/29/05-5/1/05	Request for List of investigator and sub-investigators in TPV clinical program	Ms. Anuja Patel, MPH Health Science Administrator	NA	NA	NA
4/29/05	FDA query – tables for the classification of toxicity grading for studies 0040, 0012, 0048, 0051 and 0052	Ms. Tanima Sinha Project Manager	12/6/04	A012	Response to FDA Request For Information: Comments Regarding 1182.12 study report
4/29/05	FDA query from Dr. James regarding raw or analysis datasets/CMC and pharm\tox comments should come next week	Ms. Tanima Sinha Project Manager	4/29/05	A063	Response to FDA Request For Information: datasets that will provide info on protocol violations
4/29/05	FDA request for emailed copy of amendment 058	Ms. Tanima Sinha Project Manager	4/19/05	A058	Response to FDA Request for Information – Efficacy Analysis from RESIST program

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
4/29/05	FDA query from Dr. James regarding specific individual RESIST PT lab (AST, ALT, BILI) and clinical (specifically AES, and disposition)	Ms. Tanima Sinha Project Manager	NA	NA	NA
4/27/05	FDA stat query from Dr. Bhore – A060 Protocol deviations dataset	Ms. Tanima Sinha Project Manager	060	4/19/05	Response to FDA Request for New Protocol deviation datasets
4/27/05	May 19 AVDAC meeting – contact information for industry rep	Ms. Anuja Patel, MPH Health Science	A057	4/12/05	General Correspondence: Advisory Committee Briefing Document - DRAFT
4/26/05	Discussion of CARC studies for traditional approval	Ms. Tanima Sinha Project Manager	NA	NA	NA
4/25/05	Inquiring when BIPI will receive CMC and non clinical queries for TPV	Ms. Tanima Sinha Project Manager	NA	NA	NA
4/20/05	FDA receipt of AO57 Briefing Document	Ms. Tanima Sinha Project Manager	4/19/05	A057	General Correspondence: tipranavir Advisory Committee Meeting Briefing Document - DRAFT
4/20/05 & 4/25/05	FDA receipt of 19 April AVDAC Briefing Document/FDA request for additional CD	Ms. Anuja Patel, MPH Health Science Administrator	4/19/05	A057	General Correspondence: tipranavir Advisory Committee Meeting Briefing Document - DRAFT

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
4/19/05	FDA comments on AO57 AVDAC Briefing Document	Ms. Tanima Sinha Project Manager	4/19/05	A057	General Correspondence: tipranavir Advisory Committee Meeting Briefing Document - DRAFT
4/19/05	AVDAC briefing document – solution NDA # in header	Ms. Tanima Sinha Project Manager	4/19/05	A057	General Correspondence: tipranavir Advisory Committee Meeting Briefing Document - DRAFT
4/19/05	FDA request to cancel weekly clin/stat teleconference on 20 April, 2005	Ms. Tanima Sinha Project Manager	NA	NA	NA
4/18/05	BI response to reminder that AVDAC backgrounder due 19 April	Ms. Anuja Patel, MPH Health Science Administrator	NA	NA	NA
4/18/05	FDA TPV request for patient numbers from NDA A049 (Protocol Deviations) table 4 (PTS with relevant protocol deviations for Resist 1 and Resist 2	Ms. Tanima Sinha Project Manager	4/6/05	A049	Response to FDA Request For Information: response to protocol deviation queries

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
4/15/05	TPV Peds query and DDMAC Interaction	Ms. Tanima Sinha Project Manager Dr. Rosemary Johann-Liang Medical Team Leader Dr. Melisse Baylor Medical Reviewer	4/4/05	N/A	Meeting with Division And BIPI
4/14/05	FDA stat query A052 response to April 6, 2005 stats query (genotype sensitivity score)	Ms. Tanima Sinha Project Manager	4/12/05	A052	Response to FDA Request For Information: statistical Queries from Ms. Zeballas of 4/7/05 via e-mail
4/13/05	FDA comments regarding AC Backgrounder for TPV-STATS efficacy comments	Ms. Tanima Sinha Project Manager	4/19/05	A057	General Correspondence: Tipranavir Advisory Committee Meeting Briefing Document - DRAFT
4/13/05	FDA request for telecon TPV RESIST efficacy results and outcome	Ms. Tanima Sinha Project Manager	NA	NA	NA
4/13/05	FDA follow up issues – STAT comment on April 7, 2005 query – Patient disposition	Ms. Tanima Sinha Project Manager	4/7/05	NA	Stat comments on April 7, 2005 query
4/13/05	FDA microbiology comments regarding AC briefing document	Ms. Tanima Sinha Project Manager	4/19/05	A057	General Correspondence Tipranavir Advisory Committee Briefing document - DRAFT

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
4/13/05	FDA comments regarding AC backgrounder for TPV – Clinical AE grading	Ms. Tanima Sinha Project Manager	3/24/05	A043	General Correspondence Tipranavir Advisory Committee Briefing document
4/13/05	Follow up on • Request for feedback on timing and need for updated disposition dataset • AVDAC preparation – Request for feedback on resistance package and FDA's safety presentation • Written response that final CARC studies not needed for TA	Ms. Tanima Sinha Project Manager	NA	NA	NA
4/11/05	FDA weekly clin/stat telecon regarding TPV 27 April 2005	Ms. Tanima Sinha Project Manager	NA	NA	NA
4/11/05	FDA query – comments on pediatric study report	Ms. Tanima Sinha Project Manager	NA	NA	NA
4/11/05	FDA comments on AC backgrounder 4/11/05	Ms. Tanima Sinha Project Manager	3/34/05 4/4/05	A043 meeting	DRAFT ADVAC Background document for 4/4/05 meeting meeting with FDA to review background document

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
4/4/05	Various questions/comments at side meeting during 4 April 05 BI_DAVDP meeting, importantly including the topics of Traditional Approval, Monthly Safety Reports, AVDAC Rehearsing, Meeting Participants	Ms. Tanima Sinha Project Manager	3/24/05 4/4/05	A043 NA	Background Document for 4/4/05 meeting April 4, 2005 Meeting
4/1/05	FDA request – TPV SAE fatal narratives	Ms. Tanima Sinha Project Manager	NA	NA	NA
3/30/25	FDA TPV Query from Dr. Gibbs – Trials 1182.4, 1182.6 and 1182.51/Queries on 1182.22	Ms. Tanima Sinha Project Manager	NA	NA	NA
3/23/05	Micro Requests RE varied>fold change values in pheno data/missing pheno data	Ms. Tanima Sinha Project Manager	NA	NA	NA
3/16/05	FDA comments regarding EAP and the IB for TPV – updates needed – corrected e-mail from original 3/16 query.	Ms. Tanima Sinha Project Manager	3/16/05	e-mail	FDA comments regarding EAP and the IB for TPV – updates needed
3/16/05	FDA stats query – data coding problems	Ms. Tanima Sinha Project Manager	NA	NA	NA
3/14/05	STAT queries on TPV NDA 21-814 from Dr. Bhore – data for RESIST 2 trial (study 1182.48)	Ms. Tanima Sinha Project Manager	NA	NA	NA
3/10/05	TPV query from Dr. James – Dataset Discrepancies	Ms. Tanima Sinha Project Manager	NA	NA	NA

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
3/10/05	Stat queries on TPV resist trials - OBR	Ms. Tanima Sinha Project Manager	NA	NA	NA
3/10/05	TPV ACR – AE Information for Naïve study/updated label	Ms. Tanima Sinha Project Manager	NA	NA	NA
3/9/05	Microbiology comments/information/clarification request for TPV	Ms. Tanima Sinha Project Manager	NA	NA	NA
3/4/05	FDA TPV NDA 21-814 queries – 74 day filing review issues letter	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/25/05	TPV NDA 21-814 queries regarding pharm/tox or chemistry	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/25/05	Request for Clarification of Variables referring to ITT Population	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/18/05	FDA canceling weekly clin/stat telecon-Wednesday, 2/23	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/18/05	FDA comments from Dr. Baylor for TPV Studies 1182.51 and 1182.52	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/16/05	FDA TPV request from Dr.Zhang-PK Reviewer	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/15/05	Propose Cancellation of this week's teleconference	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/14/05	FDA TPV Query from Dr. Gibbs – Trials 1182.4,1182.6 and 1182.51/Queries on 1182.22	Ms. Tanima Sinha Project Manager	NA	NA	NA

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
2/11/05	Study Reports – Phase III studies 1182.12 & 1182.48 – FDA cannot locate in NDA.	Ms. Tanima Sinha Project Manager	12/21/04	NA	Original NDA
2/9/05	FDA information requests ? 1182.51: provide measuring code in DESTERM. ? 1182.22 – Requesting temperature measurements taken during trial	Virginia Behr Chief Project Manager, DAVDP	NA	NA	NA
2/9/05	Several topics discussed- 2MSUR,IND AR, Filing Date, AVDAC prep, resistance, site inspections, responses to requests for information	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/9/05	TPV NDA – 21-814 – Participants at 4 Feb. Telecon	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/9/05	TPV NDA-21-814 AVDAC tentative meeting agenda	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/8/05	FDA Information Request from Dr. Bhore and Dr. Baylor – RESIST 1 and RESIST 2- regarding discontinuations/additions/switches of antiretrovirals on study.	Ms. Tanima Sinha Project Manager	NA	NA	NA
2/8/05	FDA Request for Info for CRF for PT #2052-Trial 1182.22	Ms. Tanima Sinha Project Manager	NA	NA	NA

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
2/4/05	Clarification of format for amendment 023/Agreement to clarify request for dataset (Question 11) in FDA's Feb 2, 2005 email request at teleconference on Feb 4, 2005	Janet Rowe Program Specialist	2/3/05	023	Response to FDA Request for information:Reformatting data for patients in the RESIST 1 and RESIST 2 Programs Background Therapy Optimization tables
2/3/05-2/4/05	Voicemail regarding NDA 21-814 for an Audit	Janet Rowe Program Specialist	NA	NA	NA
2/3/05	FDA email requesting location of information for the 1182.22 study	Virginia Behr Chief Project Manager, DAVDP	12/21/04	NA	Original NDA
2/3/05	Correction to FDA's Feb. 2, 2005 email List of Queries	Ms. Tanima Sinha Project Manager	2/2/05	FDA e-mail	Clin/Stat Queries – OBR, ARV Changes, clarification of responders
2/2/05	FDA teleconference rescheduled for Friday at 9:30/clin/stat queries – OBR, ARV changes, clarification of responders	Monica Zeballos Regulatory Project Manager	N/A	N/A	N/A
2/1/05	Teleconference Details – FDA proposing time change	Elizabeth Thompson Project Manager, DAVDP	N/A	N/A	N/A
1/28/05	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2005-BP-00649RA(0)
1/27/05	Confirm meeting arrangements for Jan. 28, 2005 teleconference	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
1/27/05	Arrangements for Jan. 28, 2005 teleconference/Dr. Bhore seeking clarification on BI responses to her recent comments	Ms. Tanima Sinha Project Manager	11/14/04	e-mail	Request from Dr. Bhore – Clarification on BI responses to her recent comments
1/11/05	Request for Database lock dates and length of patient follow up for each e-submission	Ms. Tanima Sinha Project Manager	multiple	multiple	all electronic submissions
1/10/05	Request for Weekly ClinStat teleconference between Division and BI	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
12/15/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-FF-00714FF
12/13/04	Follow up on adequacy of e-submission datasets Request for telecon to discuss NDA options on Friday, December 17, 2004	Ms. Tanima Sinha Project Manager	12/21/04	21-814	Original NDA
12/10/04	TPV NDA 21-814 amendment 014 and DSI Information	Ms. Tanima Sinha Project Manager	12/9/04	A014	Response to FDA Request For Information – updated Information on datasets
12/6/04	FDA request for clarification TPV NDA 21-814 – full master files of 1182.12/.48 and .52	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
12/6/04	FDA teleconference confirmation – 7 December with Dr. Bhore and BI	Ms. Tanima Sinha Project Manager	12/11/04	A011	N/A

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
12/6/04	#3 stat query for efficacy data on TPV for RESIST 1 and RESIST 2 studies	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
12/6/04	Materials for 7 December telecon-Biometrics & Data Management	Ms. Tanima Sinha Project Manager	Telefax 12/05/04	11/12/04 A011	Fax request from Ms. Sinha with Reviewers' comments regarding the CRT datasets Response to FDA Request for Information of TPV Datasets:
12/3/04	Timeline for e-sub datasets	Ms. Tanima Sinha Project Manager	multiple	multiple	Electronic submissions
12/02/04	FDA request issues of microbiology	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
12/02/04	FDA Submission timing/Medical server major outage	Ms. Tanima SinhaProject Manager	N/A	N/A	N/A
12/02/04	FDA Email Re: Datasets submission for TPV – If the proposed Dec 3, 04 submission of datasets is not sent to FDA by COB December 6, 04, it will affect the review of the NDA.	Ms. Tanima Sinha Project Manager	11/12/04	FDA email	Request for datasets

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
12/02/04	FDA Request TPV Clarifications Datasets confirming that the real raw datasets correspond exactly to the CRF and the submitted Clinical Study Reports and Integrated Summary of Safety	Ms. Tanima Sinha Project Manager	12/21/04	21-814	Original NDA
12/01/04	TPV Updated Datasets – Due to outage on storage area network, BIPI cannot commit to the submission of updated datasets by 12/3/04	Ms. Tanima Sinha Project Manager	11/12/04	FDA Email	Request for Datasets
11/30/04	TPV Telecon September 30th, 2004 regarding microbiology comments for SN 533 and the resistance template		7/28/04	SN 533	General Correpondence – Request for FDA Feedback – Resistance Template
11/30/04	FDA Request for contact Info. - March 10 AVDAC Meeting	Anuja Patel Executive Secretary AVDAC	N/A	N/A	N/A
11/24/04	Clin pharm questions: oral solution request for .CTL file, clarification of clin pharm study report	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
11/24/04	Called to Set-up site audits	Tony El-Hage DSI	N/A	N/A	N/A

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
11/19/04	Telecon on datasets	DAVDP	3/17/04	346	Pre-NDA meeting package
			6/18/04	471	E-sub Plan Update
			7/12/04	ACR	Telecon to discuss E-sub & Adequacy of CDISC 3.0
			9/13,16, 20/04	ACR	Patient profiler / Test DVD
11/17/04	Comments from the clinical review team –Dataset Queries	Ms. Tanima Sinha Project Manager	12/21/04	21-814	Original NDA
11/17/04	Study report query related to demographic datasets	Ms. Tanima Sinha Project Manager	12/21/04	21-814	Original NDA

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
11/17/04	FDA #1 Stat Queries for TPV NDA 21-814 – raw datasets and patient disposition file DS. Dr. Bhore needs more clarification.	Ms. Tanima Sinha Project Manager	12/21/04	21-814	Original NDA
11/12/04	FDA request for Actual Label for Packaging	Ms. Tanima Sinha Project Manager	12/21/04	21-814	Original NDA
11/5/04	FDA memo from Dr. James regarding NDA for TPV – Request for full narratives, discrepancies in fatality numbers, request for CRFs for fatal cases	Ms. Tanima Sinha Project Manager	12/21/04	21-814	Original NDA
11/5/04	Cross Referencing for SCS – deaths submission query	Ms. Tanima Sinha Project Manager	12/21/04	21-814	Original NDA
10/28/04	Cross Referencing for SCS – notified FDA that some of the cross-referencing in the Summary of Clinical Safety did not resolve correctly. BIPI will send updated volumes in an NDA Amendment.	Ms. Tanima Sinha Project Manager	12/21/04	21-814	Original NDA
10/28/04	NDA Amendment 001 – Submission Clarification	Ms. Tanima Sinha Project Manager	10/28/04	A001	Response to FDA Request for Information on TPV deaths in studies 1182.12, 1182.48, 1182.17 and 1182.58
10/25/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	10/28/04	593	IND Safety Reports (10/16/04-10/30/04) Case IW-2004-BP-08523B0

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
10/18/04	TPV "test DVD" successfully loaded by FDA	Tom Selnekovic Electronic Document Room Project Manager	N/A	N/A	N/A
10/12/04 – 10/ 13/04	Request to load "test esub DVD"	Tom Selnekovic Electronic Document Room	N/A	N/A	N/A
10/7/04	Telecon – Investigators Brochure	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
10/7/04	Immunotox Study Proposal – SN 582	Ms. Tanima Sinha Project Manager	9/23/04	582	Pharmacology/Toxicology Request for Feedback on Immunotoxicity Study Protocol
10/5/04	Electronic submission demonstration	DAVDP IT	3/17/04	346	Pre-NDA meeting package
			6/18/04	471	E-sub Plan Update
			7/12/04	ACR	Telecon to discuss E-sub & Adequacy of CDISC 3.0
			9/13,16, 20/04	ACR	Patient profiler / Test DVD
			9/27/04	583	GG E-sub demo agenda, Reviewer's guide, e-sub structure

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
10/2/04	Meeting to discuss pediatric written request	DAVDP	11/15/02 1/22/03 7/23/03	186 N/A 242	Pediatric Proposal Pediatric written request Request for changes to written request
9/24 &9/27/04	Early Submission of Module 4 – notifying FDA that BIPI Will be submitting Module 4 early.	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
9/22/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-BP-08103BP(0)
9/21/04	FDA Request for Desk copies – Treatment IND	M. Tanima Sinha Project Manager	9/7/04	Original IND 70,629	Treatment IND
9/17/04	Response to Requests – August 30th Telecon	Ms. Tanima Sinha Project Manager	318	2/20/04	GC – Request for FDA Feedback in regards to BI's plans for immunotoxicology testing for TPV
9/17/04	FDA Attendees for August 30th telecon	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
9/13,16,20, 2004	FDA's Patient Profiler Text Files	Ken Edmunds FDA/CDER/OIM	N/A	N/A	N/A
9/3/04	TPV Electronic NDA Demonstration scheduled Oct. 5, 2004 10-11:30am Submission of reports to the NDA Treatment IND – Annual Report Required	Ms. Tanima Sinha Project Manager	9/1/04	N/A	9/1/04 Telecon
9/3/04	BI Attendees for Sept. 1st Telecon	Ms. Tanima Sinha Project Manager	9/1/04	N/A	9/1/04 Telecon
9/3/04	FDA attendees from September 1st telecon	Ms. Tanima Sinha Project Manager	9/1/04	N/A	9/1/04 Telecon
9/3/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-BP-03153BR(0)
9/2/04	FDA contact regarding the 2-year rat carcinogenicity study 02R051	Dr. James Farrelly, Supervisory Pharmacologist, DAVDP	6/17/04	470	Information Amendment: PharmTox 24-Month Oral Rat Carcinogenicity Study
9/2/04	September 1st Telecon Clarification on in vitro interaction Data of TPV with APV and LPV	Ms. Tanima Sinha Project Manager	527	7/22/04	Information Amendment: Pharmacology/Toxicology (U03-3565, U03-3153)
9/1/04	Request for Information on NDA Logistics	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
8/30/04	Copies of Meeting Minutes or Faxes from important FDA/Sponsor Meetings can be included in the literature sections of Modules 3, 4 and 5.	Ken Edmunds FDA/CDER/OIM	N/A	N/A	N/A
8/31/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-BP-07145BP(0)
8/27/04	Confirmed FDA/BIPI Teleconference time extended – 12:30-2:00 pm on 30 August 2004	Mr. Destry Sullivan Project Manager FDA, CDER, Division of Antiviral Drug Products	N/A	N/A	N/A
8/26 & 8/31	FDA ESUB Coordinator provided guidance on three questions related to DVD's and their use as the media for an electronic submission	Ken Edmunds FDA/CDER/OIM	N/A	N/A	N/A
8/18/04	FDA Request for Time Change – August 30th teleconference/resistance template/pharm tox	Destry Sillivan Project Manager, DAVDP	N/A	N/A	N/A
8/16/04	Schedule Teleconference to Discuss HIV Resistance Template	Destry Sillivan Project Manager, DAVDP	N/A	N/A	N/A
8/13/04	Location of Financial Disclosure Information in NDA's	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
8/13/04	- Any electronic files that are not compliant with the file formats listed in the FDA's electronic submission guidance and submitted to the Electronic Document Room is removed from the submission before it is loaded onto FDA's Electronic Submission Server For the Tipranavir electronic submission demo, BIPI should plan on bringing a laptop loaded with the data - The esub coordination should be contacted with the request to "test load" electronic data	Gary Gensinger Supervisory Regulatory Info	N/A	N/A	N/A
8/10/04	Follow-up Electronic Submission of Clinical Report 1182.4 • Request for Response on Outstanding Business	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
8/3/04	Electronic Submission of Clinical Report 1182.4 – BIPI requesting that appendices will be submitted electronically.	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
8/3/04	Delay in submission 1182.51 study report to September 2004 Request for comment in preparation for EAP telecon on August 4, 2004 Follow up on outstanding business	Ms. Tanima Sinha Project Manager	4/15/04	383	Information Amendment – Clinical Interim Study Results of Pharmacokinetic Study 1182.51
7/30/04	Updated HIV resistance template Request for status update of feedback on microbiology submissions o Resistance template o In vitro study proposal Follow up on outstanding issues	Ms. Tanima Sinha Project Manager	7/28/04	533	General Correspondence – Request for FDA Feedback Resistance Template
7/29/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-BP-05975BP(0)
7/28/04	DVD can be used as a media for electronic submissions.	Ken Edmunds FDA/CDER/OIM	N/A	N/A	N/A
7/27/04	Obtain clarification of User Fee for upcoming NDA's for the same drug but different dosage form to be sumitted at the same time.	Ms. Beverly Friedman Office of Regulatory Policy, HFD-5	N/A	N/A	N/A
7/27/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-BP-05812BP(0)
7/22/04	Submission of New Report to NDA	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
7/22/04	BI Follow up on IND Serial Numbering	Ms. Tanima Sinha Project Manager	483	6/22/04	Type A IND Meeting-Response to FDA Pre-Meeting Request for

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
					Information-CMC-Tipranavir Oral Solution
7/20/04	- Correction of Request for Desk Copies - Confirmation of Teleconference on 3-step approach	Ms. Tanima Sinha Project Manager	7/12/04 telefax	513 6/3/04	Response to FDA Request for Information Response to Telefax from FDA Pharmacologist, Anthony ElHage-Requesting info on investigators, sites, discontinuations and reasons discontinuations for all of the pivotal sties for TPV Trials (1182.12, 1182.48 and 1182.14
7/16/04	Teleconference Between BIPI and FDA on July 19, 2004 Attendees	Ms. Tanima Sinha Project Manager	7/1/04	501	General Correspondence /Request for FDA Feedback /Request for Teleconference NDA Clinical Summary Cross-Referencing Plan Presentation of Patient Disposition, Clinical Summary y Integration Plan
7/16/04	SN 315 (Clinical Information Amendment-Safety) Desk Copies	Ms. Tanima Sinha Project Manager	2/18/04	315	Information Amendment – Clinical Safety Information • 2004-FF-00088FF(0)

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
7/13/04	FDA Request for Desk Copies – SN 501	Ms. Tanima Sinha Project Manager	7/1/04	501	General Correspondence/Request for FDA Feedback/Request for Teleconference NDA Clinical Sumary Cross Referencing Plan, Presentation of Patient Disposition, Clinical Summary Integration Plan

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
7/12/04	Telcon to discuss E-submission and adequacy of CDISC 3.0	Ms. Tanima Sinha Project Manager, DAVDP, IT	3/17/04 6/18/04 6/11/04	346 471 ACR	Pre-NDA background document E-submission plans update Request for feedback on e-sub plans
7/9/04	Submission of New Reports to NDA	Ms. Tanima Sinha Project Manager	Pre-Nda Meeting Telecon	6/2/04 6/28/04	E-mail follow up regarding submission of new reports to NDA Discussion of New Reports being submitted to NDA.
7/9/04	Follow up on Submission SN 501-Scheduling of Telecon	Ms. Tanima Sinha Project Manager	7/1/04	501	General Corespondence/Request for FDA Feedback /Request for Teleconference NDA Clinical Summary Cross-Referencing Plan Presentation of Patient Disposition, Clinical Summary Integration Plan
7/9/04	BI Attendees for July 12, 2004 teleconference	Ms. Tanima Sinha Project Manager	N/A	N/A	Teleconference to discuss electronic submission proposal and request for information on the TPV NDA
7/9/04	• In vitro interaction studies w/ARV's request for desk copies	Ms. Tanima Sinha Project Manager	6/29/04	496	Information Amendment:Clinical – Step 1 of Drug Interaction Study

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
7/9/04	Proposal for in vitro studies with ARV's Electronic Submission Proposal Teleconference attendees	Ms. Tanima Sinha Project Manager	6/29/04 6/18/04	496 SN 346	Information Amendment Clinical – Step 1 of Drug Interaction Study Electronic Submission Proposal
7/8/04	BI Request for FDA Attendees for Telecon	Ms. Tanima Sinha Project Manager	N/A	N/A	BI Request for FDA Attendess for July 12, 2004 Telecon re: TPV Electronic Submission
7/7/04	Request for Desk Copies of SN496	Ms. Tanima Sinha Project Manager	6/30/04	496	General Correspondence Minutes of June 7, 2004 Teleconference
7/6/04	BI Request for Teleconference to discuss Step 1 of Drug Interaction Analysis	Ms. Tanima Sinha Project Manager	6/30/04	496	General Correspondence Minutes of June 7, 2004 Teleconference
7/1/04	TPV IND Serial Numbering BIPI used SN 483 twice: FDA stated not to change	Ms. Tanima Sinha Project Manager	6/22/04	483	Type A IND Meeting Response.
7/1/04	FDA Comments on SN 470 Termination of Dosing Group in Rat Care Study Scheduling Telecon for Step 1 of 3-step DI Analysis	Ms. Tanima Sinha Project Manager	6/17/04	470	Information Amendment: PharmTox 24-Month Oral Rat Carcinogenicity Study
6/30/04	Postponement of Tradename Evaluation	Ms. Tanima Sinha Project Manager	2/6/04	307	General Correspondence – Request for Evaluation of Trade name
6/29/04	Template for Resistance Data	Ms. Tanima Sinha Project Manager	N/A	N/A	Ms. Sinha sent latest template for submitting HIV Resistance Data

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
6/28/04	Confirmation of Teleconference to discuss Electronic Submission Proposal	Ms. Tanima Sinha Project Manager	N/A	N/A	Teleconference confirmation
6/24/04-6/28/04	Follow up on outstanding business; • Procedural (IND SNs, NDA Number, Electronic Submission Plan • Clinical (Patient Disposition Plans for NDA, DI Analysis 3-step Approach, Integration Plans, IND Annual Report/2-month Safety Update Plan, Clinical Summaries Cross-Referencing Plan) • Nonclinical (Rat Carc., Immunotox, In vitro Resistance, Resistance Template/Presentation of Microbiology in CTD)	Ms. Tanima Sinha Project Manager	6/17/04	470	Information Amendment: PharmTox 24-Month Oral Rat Carcinogenicity Study

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
6/18/04	FDA Comment on Export Authorization Request/Protocol	Rosemary Johann-Liang, MD Medical Team Leader with Tanima Sinha, Project Manager and Andrea James, MD, Medical Reviewer			Export Waiver
6/17/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-BP-04608BP(0)
6/17/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-FF-00364FF(0)
6/17/04	Call placed informing 7-Day Safety Report would be faxed. Resend 6/10 fax	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-UK-00526UK(0) RESENT
6/16/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-BP-04500RA(0)
6/14/04	Electronic Submission Specifics	Rosemary Johann-Liang, MD Medical Team Leader	6/11/04	460	Information Amendment – Type A IND Meeting Package
6/11/04	FDA request for feedback on FDA request for additions to Electronic Submission Plan	General Division Voicemail	N/A	N/A	May 10th 2004 pre-NDA Telecon

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
6/10/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-UK-00526UK(0)
6/10/04	FDA Project Manager Away from Office	Ms. Tanima Sinha Project Manager, DAVDP	N/A	N/A	N/A
6/3/04	FDA request for discussion of like analyses core cases 2004BP03721 and 2004BP03614BR at Monday, June 7, 2004 Teleconference	Ms. Tanima Sinha Project Manager, DAVDP	5/24/04	SN 431 & SN 432	Like analyses core cases 2004BP03721 and 2004BP03614BR
5/10/04, 6/2/04	Clinical /Nonclinical Pre-NDA Meeting (Telecon 5/10, Face to Face 6/2)	DAVDP	3/17/04	346	Pre-NDA Package
5/27/04	FDA request summary info regarding food effects on bioavailability of SEDDS formulation in humans	Ms. Tanima Sinha Project Manager, DAVDP	5/28/04	445	Information Amendment Clinical Food Effect
5/27/04	FDA reminder request of May 7 to summarize at the pre-NDA meeting the RESIST protocol and amendments and the impact of each amendment on the statistical analysis plan	Ms. Tanima Sinha Project Manager, DAVDP	3/17/04	346	General Correspondence – Pre-NDA Meeting Package Request for Teleconference to Discuss key clinical, statistical and format topics prior to face-to-face meeting
5/27/04	FDA request- from Dr. Zhang, Clinical Pharmacology reviewer for Tipranavir regarding SEDDS formulation in humans	Ms. Tanima Sinha Project Manager, DAVDP	N/A	N/A	N/A

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
5/27/04	SN 375 & 401 FDA requesting updated lab info, specifically bilirubins	Ms. Tanima Sinha Project Manager, DAVDP	4/12/04 5/3/04	375 401	IND Safety Report Initial Report 2003-BP-03027BP(0) IND Safety Report Follow-up 2003-BP-09788BR(3)
5/27/04	FDA Request-summarize RESIST protocol & amendments-impact of each amendment on the statistical analysis plan for TPV	Ms. Tanima Sinha Project Manager, DAVDP	3/17/04	346	General Correspondence – Pre-NDA Meeting Package Request for Teleconference to Discuss key clinical, statistical and format topics prior to face-to-face meeting
5/21/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager, DAVDP	N/A	N/A	2004-BP-03787BP(0)
5/21/04	Safety Reporting Process teleconference scheduling on June 7, 2004 – Pre NDA meeting plans/submission of RESIST Data	Ms. Tanima Sinha Project Manager, DAVDP	5/21/04	427	General Correspondence – Request for Teleconference – Update of Safety Reporting Procedures
5/11/04	Follow up on submission SN 318/Immunotox Proposal	Ms. Tanima Sinha Project Manager, DAVDP	2/20/04	318	General Correspondence – Request for FDA Feedback in regards to BI's plans for immunotoxicology testing for Tipranavir
5/10/04	FDA out of office notification	Ms. Tanima Sinha Project Manager, DAVDP	N/A	N/A	N/A

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5/7/04	BI Attendees for May 7, 2004 teleconference	Ms. Tanima Sinha Project Manager, DAVDP	5/7/04	N/A	teleconference
5/7/04	FDA request to briefly summarize the original RESIST protocol amendment	Ms. Tanima Sinha Project Manager, DAVDP	3/17/04	346	General Correspondence – Pre-NDA Meeting Package Request for Teleconference to Discuss key clinical, statistical and format topics prior to face-to-face meeting
5/6/04	FDA Attendees for May 7, 2004 teleconference	Ms. Tanima Sinha Project Manager, DAVDP	N/A	N/A	FDA attendees for May 7, 2004 teleconference
5/5/04	Background Information for Friday May 7, 2004 Teleconference	Ms. Tanima Sinha Project Manager, DAVDP	4/15/04	384	Response to Request for Information/Request for Teleconference
5/4/04	FDA Request for Desk copies SN303/SN392	Ms. Tanima Sinha Project Manager, DAVDP	2/6/04 4/22/04	303 392	IND Annual Report – Reporting period 10/1/02-9/30/03 Response to Request for Information: Tabular Listing of Deaths
4/29/04	Follow up on Submission SN318-February 20, 2004 Immunotox Proposal	Tanima Sinha Project Manager DAVDP	2/20/04	318	General Correspondence – Request for FDA Feedback in regards to BI's plans for immunotoxicology testing for Tipranavir

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
4/26/04	TPV FDA Teleconference to address responses to April 8, 2004 Fax	Ms. Tanima Sinha Project Manager, DAVDP	4/22/04	392	Response to Request for Information: Tabular Listing of Deaths
4/16/04	Telecon arrangements discuss responses to April 8/04 Fax (feedback on interim results from study 1182.51)	Tanima Sinha Project Manager, DAVDP	4/15/04	383	Information Amendment: Clinical Interim study results of pharmacokinetic study 1182.51
4/9/04	Respond to request for info (PK Study 1182.51 Methods/Procedures for a Proposal to examine the possible effects of medication on HIV-related death in TPV trials	Ms. Tanima Sinha Project Manager, DAVDP	4/15/04	383	Information Amendment: Clinical Interim Study Results of pharmacokinetic study 1182.51
4/9/04	Advise Division of plans to respond to April 8, 2004 fax	Tanima Sinha Project Manager, DAVDP	4/8/04 4/15/04	FDA Fax 383	Fax regarding pharmacokinetic Study 1182.51 IA Clinical – Interim Study Results of pharmacokinetic Study 1182.51
4/8/04	Fax regarding Pharmacokinetic Study 1182.51	Rosemary Johann-Liang, MD Medical Team Leader (with Tanima Sinha, Project Manager and Andrea James, MD, Medical Reviewer	N/A	N/A	Telephone contact – FDA informing of a fax being sent regarding the Pharmacokinetic Study 1182.51

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
4/7/04	Mtg to discuss update to safety reporting processes and procedures (sn 369)/timing of pre-NDA Mtg&Telecon	Ms. Tanima Sinha Project Manager, DAVDP	4/6/04	369	General Correspondence – Background/Current Safety Reporting Processes and Procedures and Proposed updates to Safety Reporting Processes and Procedures Request for Teleconference to assure that BI can implement the new Processes and Procedures
4/2/04	Timing for Pre-NDA teleconference	Ms. Tanima Sinha Project Manager, DAVDP	3/12/04 & 3/26/04	Agency Contacts	Timing for Pre-NDA teleconference
4/2/04	FDA Request for Desk Copies of CMC Pre-NDA Meeting Package SN 349	Ms. Tanima Sinha Project Manager, DAVDP	3/19/04	349	Information Package for Type B Pre-NDA Meeting - CMC
3/31/04	Informed that 2 7-day safety reports would be faxed.	Ms. Tanima Sinha Project Manager, DAVDP	N/A	N/A	2004-BP-02413AU(0) 2003-BP-10433BP(0)
3/26/04	Scheduling of Pre-NDA Meeting	Ms. Tanima Sinha Project Manager, DAVDP	3/12/04	Agency Contact	Scheduling of Pre-NDA Meeting
3/17/04	Request for desk copy of RESIST Protocol.	Ms. Tanima Sinha Project Manager	3/17/04	441	General Correspondence: Statistical Analysis Plan – submitting the summary of the RESIST Protocol

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
3/17/04	Follow-up on previous discussions about setting up a meeting.	Ms. Tanima Sinha Project Manager	N/A	N/A	N/A
3/16/04	Attention fax about 7-day safety reports being sent.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-BP-00176-FF(0) 2004-BP-00953BP(0) 2004-FF-00180FF(0) 2004-BP-01840BP(0)
3/15/04	Attention fax about 7-day safety reports being sent.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-BP-01767BP(0) 2004-BP-10562BP(0)
3/15/04	Mortality Analysis Submission, Request for Teleconference, and Pre-NDA Meeting Timing.	Ms. Tanima Sinha Project Manager	3/12/04	340	Response to FDA Request – Review of Mortality Rates Request for Teleconference to discuss this information, answer any questions and receive feedback
3/11/04 & 4/2/04	Inform FDA decision to hold separate pre-NDA meeting for oral solution. Confirm that CMC pre-NDA meeting will be 2 hrs long, ask about new Chemistry Reviewer	Ms. Tanima Sinha Project Manager	2/17/04	314	Request for Type B Meeting – CMC Pre-NDA Meeting
3/12/04	Advisory of sending an electronic copy of a submission providing a Mortality Assessment of the tipranavir RESIST program.	Ms. Tanima Sinha Project Manager		276	Information Amendment – Clinical Request for FDA Comments on Special Protocol Assessment for Protocol 1182.12 (RESIST 1)

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
3/9/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2003-BP-04672BP(1) 2003-FF-00625FF(0)
3/5/04	Request from FDA regarding mortality rates and publication discussed at Feb 19, 2004 telecon.	Ms. Tanima Sinha Project Manager	2/19/04	N/A	February 19, 2004 teleconference regarding mortality rates and publication
3/3/04 2/20/04	Request for desk copies of SN 307, Proposed Trade name submission and feedback on timing for response to trade name evaluation submission.	Ms. Tanima Sinha Project Manager	2/6/04	307	General Correspondence – Request for Evaluation of Trade name
2/24/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	204-SW-00048SW(0)
2/23/04	Call placed informing 7-Day Safety Report would be faxed.	Ms. Tanima Sinha Project Manager	N/A	N/A	2004-FF-00105FF
2/20/04	Email attachment with BI Attendees for 2/19/04 Teleconference.	Ms. Tanima Sinha DAVDP	2/19/04	N/A	February 19, 2004 teleconference
2/19/04	FDA Attendees and agenda for Feb 19, 2004.	Ms. Tanima Sinha DAVDP	1/7/04 1/12/04 1/20/04	278 281 288	General Correspondence – Response to Statistical Comments to Protocol 1182.12 (RESIST 2) Amendment 2 IND Safety Report IND Safety Report
2/18/04	Email requesting all future export waiver requests be sent to David Kelly rather than Michele Limoli.	David Kelly, International Affairs	N/A	N/A	Export waivers

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
2/18/04	To alert CSO that a request for a CMC pre-NDA meeting package had been submitted and to get an idea when meeting to be held.	Tanima Sinha, CSO FDA	2/17/04	314	Request for Type B Meeting – CMC Pre-NDA Meeting
2/13/04	Call placed informing 7-Day Safety Report would be faxed.	Tanima Sinha, Project Manger	N/A	N/A	2004-BP-01039BP(0) 2004-FF-00088FF(0) 2004-BP-00954BP(0)
2/12/04	FDA response to request for pre-NDA meeting for tipranavir.	Ms. Tanima Sinha Project Manager	1/30/04	297	Request for Type B Meeting – Pre-NDA meeting request
2/9/04	Call placed informing 7-Day Safety Report would be faxed.	Tanima Sinha, Project Manager	N/A	N/A	2004-BP-00825BR 2004-IT-00012IT
2/6/04	Contact information at DAVDP.	Ms. Virginia Behr Acting Project Manager	N/A	N/A	N/A
2/6/04	BI's plans for monthly safety update report, request for feedback regarding Pre-NDA Meeting request and contact information in Nancy McKay's absence.	Ms. Virginia Behr Acting Project Manager	2/2/04 1/30/04	299 297	General Correspondence – drafted revision to corporate Standard Operating Procedures (SOPs) regarding adverse event reporting Request for Type B Meeting – Pre-NDA meeting request
2/5/04	Degrees/titles for BIPI participants of January 16, 2004 meeting.	Ms. Virginia Behr Acting Project Manager	1/16/04	N/A	January 16, 2004 meeting
2/3/04-5/04/04	Information from BI regarding the teleconference for Feb 19, 2004.	Ms. Virginia Behr Acting Project Manager	1/7/04	278	General Correspondence – Response to Statistical Comments to Protocol 1182.12 (RESIST 1) Amendment 2

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
2/2/04	• Call placed informing 7-Day Safety Report would be faxed. • Also, Virginia gave new fax number.	Ms. Virginia Behr Acting Project Manager	N/A	N/A	Case # 2003-BP-00677BP(0)
2/2/04	• Confirmation of sending the safety reporting procedures submission. • FDA Request for teleconference to discuss expedited reporting and like analysis on hepatotox report and BI's response to statistical comments regarding RESIST-1.	Ms. Virginia Behr Acting Project Manager	2/2/04	299	General Correspondence – drafted revision to corporate Standard Operating Procedures (SOPs) regarding adverse event reporting
1/30/04	Status of BI's progress with agreements made at Jan 16, 2004 meeting.	Ms. Virginia Behr Acting Project Manager	2/5/04 1/16/04	302 telecon	General Correspondence – BI Meeting minutes from face to face meeting – January 16, 2004 Teleconference regarding Safety reporting
1/28/04	BIPIs electronic presentations from 1/16/04 face-to-face meeting. Request for copy of FDA presentation.	Virginia Behr, DAVDP	N/A	N/A	BIPIs electronic presentations from 1/16/04 face-to-face meeting. Request for copy of FDA presentation
1/27/04	• Call placed informing 7-Day Safety Report would be faxed.	Virginia Behr, DAVDP	N/A	N/A	Case # 2003-BP-08944BP

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
1/15-16/04	FDA inquiry about status of Cremphor EL study and request for slides for meeting presentations.	Ms. Virginia Behr Acting Project Manager	9/26/03 1/13/04	255 Agency Contact	Information Amendment – Pharmacology/Toxicology – 26 week Safety Study of TPV/RTV SEDDS in Beagle Dogs – 13 week draft interim report Tox data
1/15/04	Email attachment with FDA attendees for 1/16/04 face-to-face meeting.	Virginia Behr, DAVDP	N/A	N/A	N/A
1/14/04	FDA confirmation of receipt of SN 285.	Virgina Behr, DAVDP	1/14/04	285	Response to FDA request for information – Safety Policies and TPV Risk Benefits
1/13/05	FDA Attendees for 1/9/04 teleconference	Virgina Behr, DAVDP	1/9/04	N/A	FDA telecon
1/13/04	Toxicology data for meeting between BI and FDA on January 16, 2004.	Ms. Virginia Behr Project Manager	9/26/03	255	Information Amendment – Pharmacology/Toxicology – 26 week Safety Study of TPV/RTV SEDDS in Beagle Dogs – 13 week draft interim report

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
1/12/04	FDA called to inquire about the status of the 26 week dog study.	Ms. Virginia Behr Project Manager	5/17/02	150	Response to FDA request for information-providing information on the in-life data at 3 months from the ongoing six-month rat and dog toxicology studies, the oral toxicity of polyoxyl 135 castor oil in animals and SEDDS formulations used for other drugs in preclinical/clinical trials
1/9/04	Change of reporting period for the FDA request for Safety Information	Virginia Behr, DAVDP	1/7/04	277	General Correspondence Safety Information for January 8, 2004 Telecon
1/9/04	Status of SN 279 Response to FDA Request for Safety Information.	Virginia Behr, DAVDP	1/9/04	279	Response to Request for Information – Aes and SAEs
1/8/04	Names, titles and degrees for FDA and BIPI participants of 1/8/04 teleconference.	Virgina Behr, DAVDP	1/8/04	N/A	Teleconference regarding Safety reports from Abbott on RTV
1/8/04-1/9/04	FDA Request for information-AEs and SAEs (change in due dates of submissions).	Virginia Behr, DAVDP	1/7/04	277	General Correspondence Safety Information for January 8, 2004 Telecon

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
1/7/04	BI called BI to advise the DAVDP that a submission will be emailed in preparation for Jan 8 04 teleconference to discuss ritonavir safety reports.	Ms. Tanima Sinha Project Manager	1/7/04	278	General Correspondence – Response to Statistical Comments to Protocol 1182.12 (RESIST 1) Amendment 2
1/5-6/04	FDA called to inform BI about unsubmitted serious adverse events and would like a teleconference to discuss the details.	Ms. Tanima Sinha Project Manager	1/6/04	N/A	Email from Tanima Sinha regarding reports from Abbott including deaths submitted.
12/31/03	BI called FDA to inform them of the upcoming Pre-NDA Meeting Request.	Ms. Tanima Sinha Project Manager	1/30/04	297	Request for Type B Meeting – Pre-NDA Meeting
12/23/03	BI email FDA asking for clarification of the labeling statement, "Caution – New Drug – Limited by Federal (or United States) law for investigational use."	Mr. David Kelly International Affairs	N/A	N/A	N/A
11/14/03	BI contact FDA for clarification of approvals for export waivers for 1182.14 and 1182.17.	Mr. David Kelly International Affairs	N/A	N/A	Export waivers
11/12/03	FDA requesting summary of long term results for BI Trial 1182.52.	Ms. Tanima Sinha Project Manager	11/07/03	FDA Request	FDA request for summary of long-term results for the 1182.52 trial

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
11/10/03	FDA called to ask where tipranavir capsules were manufactured for purposes of export waiver review.	Ms. Betty McRoy Office of Compliance	N/A	N/A	Export waivers
11/7/03	FDA Request for long-term results for 1182.52.	Tanima Sinha Project Manager	N/A	N/A	N/A
10/27/03-10/30/03	Email regarding export waiver clarification and request from microbiology team leader.	Tanima Sinha, Div. of Antiviral Drug Products	N/A	N/A	Export waivers
10/24/03	Confirmation that desk copies of the naïve special protocol assessment will be sent today. Request clarification regarding hold on export waiver requests for 1182.14 study.	Tanima Sinha, Project Manager	9/26/03	254	Request for Special Protocol Assessment – Clinical, Naïve Trial 1182.33 Export waivers
10/24/03	Request for summary on in vitro selection on virus resistance to TPV.	Tanima Sinha, Project Manager	11/20/03	265	Information Amendment – Clinical, Response to FDA Request for information On in vitro Selection of Virus Resistant to Tipranavir

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
10/20/03	Email regarding status of review for Tipranavir Export Waiver Request for 1182.14-Argentina, Brazil, Mexico, and Russia.	Tanima Sinha, DAVDP	10/16/03 10/8/03-10/6/03 8/20/03	Agency Contact Agency Contact N/A	Export waiver – previous request for status update Export waiver – previous request for status update Export waiver
10/16/03	Follow-up on with DAVDP on status of review for Tipranavir Export Waiver Request for 1182.14-Argentina, Brazil, Mexico, and Russia.	Tanima Sinha, DAVDP	8/20/03 10/6/03-10/8/03	N/A Agency Contact	Export waiver. Request for Status update
10/06/03-10/08/03	Status of review for tipranavir export waiver request for 1182.14 – Argentina, Brazil Mexico and Russia Change of personnel from Ms. Anne Norris and Mr. David Kelly in IAS	Tanima Sinha, DAVDP, Betty McRoy, OC, David Kelly, IAS, Elizabeth Duvall, OND	8/20/03	N/A	Export Waiver

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
9/26/03-9/29/03	Status of approval for tipranavir export waiver request for 1182.17-Argentina.	Betty McRoy, OC Anna Noris, IAS	6/6/03	N/A	Export waiver for 1182.17 Argentina
9/24/03	Missing pages from New Investigator Submission. Confirmation of teleconference info. for Pediatric written agreement telecon.	Tanima Sinha, Project Manager	9/12/03 9/24/03 9/22/03 9/17/03 7/23/03	250 ACR's (2) ACR ACR SN 242	Protocol Amendment – New Investigators 1182.12-1182.17-1182.24-1182.51 Administrative Info for Telecon Administrative Info for Telecon Administrative Info for Telecon Pediatric Written Agreement
9/24/03	Administrative information for the telecon to discuss BI's Pediatric Written Agreement. Call in info & BI attendee list for Oct. 2, 2003 telecon	Tanima Sinha, Project Manager	7/23/03	242	Pediatric Written Agreement
9/24/03	Confirmation to reschedule telecon for proposed Pediatric Written Agreement time of 10/2/03, 1-2 pm. Advised that Call-In info. Remained same for telecon.	Tanima Sinha, Project Manager	9/17/03 & 9/22/03	Agency Contact	Confirmation of teleconference and data – October 2, 2003, 1-2:00pm
9/22/03	Telecon to discuss BI Pediatric Written Agreement date/time negotiation.	Tanima Sinha, Project Manager	7/23/03 9/17/03 8/27/03	242 ACRs (2) ACR	Pediatric Written Agreement Admin. Info for telecon Confirm date for Telecon

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
9/17/03	Call-In Information for the teleconference to discuss BI's Proposed Pediatric Written Agreement.	Tanima Sinha, Project Manager	7/23/03 8/27/03	242 ACR	Pediatric Written Agreement Confirm date for Telecon
9/17/03	BI Attendees for teleconference on 9/18/03.	Tanima Sinha, Project Manager	N/A	N/A	N/A
9/12/03-9/15/03	Status of Tipranavir Export Waiver Request for 1182.17-Argentina.	Tanima Sinha, DAVDP Betty McRoy, OC Beth Duvall, OND	6/6/03 9/6/03-9/8/03 8/23/03-8/29/03 8/6/03-8/8/03 8/12/03-8/15/03 7/31/03-8/15/03	N/A ACR ACR ACR ACR ACR	Export waiver – 1182.17 for Argentina Request for status of export waiver Request for status of export waiver Request for status of export waiver Request for status of export waiver Request for status of export waiver

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
9/6/03-9/8/03	Status of Tipranavir Export Waiver Request for 1182.17-Argentina.	Betty McRoy, OC	6/6/03	N/A	Export waiver – 1182.17 for Argentina
			8/23/03-8/29/03	ACR	Request for status of export waiver
			8/6/03-8/8/03	ACR	Request for status of export waiver
			8/12/03-8/15/03	ACR	Request for status of export waiver
			7/31/03-8/15/03	ACR	Request for status of export waiver
9/5/03-8/31/03	Status of Tipranavir Export Waiver.	Betty McRoy, OC		N/A	Export Waiver -
8/27/03	FDA confirms date for telecon to discuss BI Pediatric Written Agreement – 9/18/03 11 am	Tanima Sinha, Project Manager	7/23/03	242	Pediatric Written Agreement
			8/26/03	ACR	Proposed date of telecon
			8/15/03	ACR	Request for telecon
8/26/03	Email with proposal dates for planned telecon between BI and FDA regarding BI's pediatric written agreement.	Tanima Sinha, Project Manager	7/23/03	242	Pediatric Written Agreement
			8/19/03-8/21/03	ACR	Request for telcon
			8/15/03	ACR	Request for telecon

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
8/25/03-8/29/03	Status of approval for Tipranavir Export Waiver Request for 1182.17 – Argentina	Betty McRoy, OC Anna Norris, IAS	6/6/03 8/6/03-8/8/03 8/12/03-8/15/03 7/14,15,23, 29/03	N/A ACR ACR ACR	Export Waiver 1182.17 Argentina Request for status of export waiver Request for status of export waiver Request for status of export waiver
8/19/03-8/21/03	Request for telecon to discuss BI Pediatric Written Agreement.	Tanima Sinha, Project Manager	7/23/03	242	Pediatric Written Agreement
8/15/03	• Request of additional copies of the RESIST 1 protocol amendments • Inquired about telecon between BI and FDA reg: BI's written agreement for pediatric studies	Tanima Sinha, Project Manager	3/19/03 3/31/03 6/10/03 7/23/03	214 220 230 242	Resist 1 Protocol Amendments Amendments 1&2 Amendment 3 Amendment 4 Pediatric Written Agreement
8/12/03-8/15/03	Status of Tipranavir Export Waiver Request – 1182.17 Argentina	Tanima Sinha DAVDP Betty McRoy, OC Beth Duvall, OND	6/6/03 8/6/03-8/8/03 7/14,15,23, 29/03	N/A ACR ACR	Export Waiver 1182.17 Argentina Request for status export waiver Request for status of export waiver

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
8/6/03-8/8/03	Status of Tipranavir Export Waiver Request – 1182.17 Argentina	Betty McRoy Office of Compliance Tanima Siha DAVDP	6/6/03 7/31/03-8/5/03 7/14,15,23, 29/03	N/A ACR ACR	Export Waiver 1182.17 Argentina Request for status of export waiver Request for status of export waiver
7/31/03-8/5/03	Status of Tipranavir Export Waiver – 1182.17 Argentina.	Betty McRoy, Office of Compliance	6/6/03 7/14,15,23, 29/03	N/A ACR	Export Waiver 1182.17 Argentina Request for status of export waiver
7/18/03	Mechanism for submission of naïve protocol for FDA feedback • Discussed whether the protocol should be submitted as a Special Protocol Assessment or an Information Amendment Response to pediatric written request planned; teleconference to be requested • Submission to be sent week of 21 July 03 • BIPI requests a telecon be scheduled to discuss the written request	Tanima Sinha, Project Manager	11/15/02 7/15/03 7/23/03	186 ACR 242	General Correspondence – Background Document for End of Phase II Meeting Request for confirmation of Spec Protocol Assess as mechanism for review of naive protocol. Proposed Changes in Written Request for Pediatric Studies/Proposed Written Agreement for Pediatric Studies\Request for Teleconference

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
7/15/03	Request for confirmation of Special Protocol Assessment as Mechanism for review of Naïve Protocol.	Tanima Sinha, Project Manager			
7/14,15,23,29/03	Requesting Status of Export Waiver Requests for 1182.17 - Argentina	Anna Norris, IAS Betty McRoy, OC	6/6/03	N/A	Export Waiver – 1182.17 Argentina
6/10/03-6/24/03	Email re: information on patient reported outcomes.	Jane Scott, PhD	N/A	N/A	E-mail correspondence
6/5/03	Request status of approval for 1182.48 (Argentina)	Anna Norris Office of International Affairs	3/12/03 5/8/03 4/8/-11/03	N/A ACR ACR	Export Waiver – 1182.48 Argentina DAVDP's review of export waiver Export Waiver Status
6/2-4/03	Request status of export waiver requests for 1182.48 for Mexico (submitted on March 14, 2003) and Brazil (submitted on March 12, 2003).	Anna Norris Office of International Affairs	3/12/03 3/14/03 5/8/03 4/8-11/03	N/A N/A ACR ACR	Export Waiver Request – Brazil 1182.48 Export Waiver Request – Mexico 1182.48 DAVP Review Status of export Waiver Export waiver status
5/21/03	Status of the CAC review of mouse carcinogenicity study	Tanima Sinha, Project Manager	3/24/03 5/20/03	216 ACR	Request for Special Protocol Assessment-Carcinogenicity Study Protocol. BI asking FDA concurrence with the mouse carcinogenicity study protocol Request for Feedback on SN 216

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
5/20/03	Request for feedback on SN 216 Request for SPA – Carcinogenicity Protocol submitted 3/24/03.	Tanima Sinha, Project Manager	3/24/03	216	Request for Special Protocol Assessment-Carcinogenicity Study Protocol. BI asking FDA concurrence with the mouse carcinogenicity study protocol
5/8/03	• DAVDP asked that BI resolves serial number discrepancy directly with document control room • Introduction of new project manager, Tanima Sinha • Full or draft protocols should be included in export waiver request when possible • DAVDP's review of export waiver requests for 1182.48 (Argentina/Mexico) is complete and has been further processed within FDA • Follow-up responses on FDA comments on 1182.51 protocol • Medical reviewer denied the need for a change in the official EOP II Meeting Minutes	Virginia Yoerg, Regulatory Health Project Manager Tanima Sinha, Regulatory Health Project Manager	4/28/03 3/24/03 3/14/03 1/30/03 5/9/03	ACR 217 N/A 204 226	SN Discrepancy EoP2 Mtg Minutes (BIPI) FDA EoP2 Mtg Minutes 1182.51 Protocol Protocol Amendments 1&2 1182.51

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
5/7/03	DAVDP clarified that it is not necessarily mandatory to submit the protocols in their entirety when request export waivers, however, it is strongly encouraged for all pivotal trials.	Virginia Yoerg, Regulatory Health Project Manager	N/A	N/A	Export waiver
5/5/03	DAVDP requested full copy of RESIST 2 protocol in order to review BI's request for export waivers for 1182.48 Serial Numbers discrepancy is still under review.	Virginia Yoerg, Regulatory Health Project Manager	11/15/02 4/22-4/28 4/18/03	186 ACR ACR	General Correspondence – Background Document for end of Phase II Meeting DISCREPENCY WITH SERIAL NO.'S
4/28/03	Email to FDA clarifying serial number discrepancy.	Virginia Yoerg, Regulatory Health Project Manager	4/22-4/28 4/18/03	ACR ACR	DISCREPENCY WITH SERIAL NO.'S
4/28/03	FDA faxed over serial number 212 for clarification of serial number discrepancy. EMail requesting agreement in that letter should have not received a serial number.	Virginia Yoerg, Regulatory Health Project Manager	4/22/-4/28 4/18/03	ACR ACR	DISCREPENCY WITH SERIAL NO.'S
4/22/03	Export Authorization Request Status for IAS-D-3-3-17 and IAS-D-3-3-18.	Andrea Chen, Office of New Drugs	N/A	N/A	N/A

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
4/22-28/03	Clarification of Serial Number discrepancy.	Virginia Yoerg, Regulatory Health Project Manager	4/18/03	ACR	DISCREPENCY WITH SERIAL NO.'S NO SUBMISSION
4/18/03	Serial Number discrepancy: FDA's serial numbers differ from BI's. Export Waiver Request Review Status: Medical reviewer currently reviewing export authorization request.	Virginia Yoerg, Regulatory Health Project Manager	N/A	N/A	DISCREPENCY WITH SERIAL NO.'S NO SUBMISSION
4/14/03	Export Waiver Status/Review of FDA Internal. Export Waiver Process and Timing.	Betty McRoy, Office of Compliance Andrea Chen, Office of New Drugs	4/14/03 4/8/03 4/11/03	N/A ACR ACR	TPV Export Waiver Status/Review of FDA internal export waiver review process and timing. #IAS-D-3-3-17/IAS-D-3-3-18
4/8-11/03	Export Waiver Approval for 1182.48. (Mexico/Argentina) Status – Expected in late May/early June.	Michelle Limoli and Anne Norris FDA, International Affairs			
3/27/03	Pam C. followed up on the 12/11/02 submission reg: designation of starting materials and on action item form the EOPII meeting reg: designation of Ph. Eur. Procedures as alternate procedures.	Virginia Yoerg, Regulatory Health Project Manager	12/11/02	191	General Correspondence-chemistry, manufacturing and controls, BI providing current specifications for 2 TPV and information regarding M-nitropropriophenone (m-NPP)

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
3/21/03	Left voice mail with FDA re design of the drug interaction study with atorvastatin (SN 206). Call was returned advising draft reviews almost completed & that they would contact us when finished.	Virginia Yoerg, Regulatory Health Project Manager	2/7/03 3/5/03	206 ACR	General Correspondence – Request for FDA Feedback regarding drug interaction study between Tipranavir and Atorvastin Comment on Atorvastatin Study
3/5/03	Called FDA for 1) clarification of SPA of carcinogenicity protocols within the DAVDP and 2) for comment on S/N 206 re design of the drug interaction study with atorvastatin.	Virginia Yoerg, Regulatory Health Project Manager	2/7/03 2/6/03	206 ACR	General Correspondence – Request for FDA Feedback regarding drug interaction study between Tipranavir and Atorvastin
3/4/03	Verbal response from FDA approving our proposal to study oral Cremophor.	Virginia Yoerg, Regulatory Health Project Manager	12/13/02 2/6/03	196 ACR	General Correspondence – Request for FDA Feedback regarding proposal for the study of oral Cremophor EL human exposure Status request on feedback for CrEl human exposure
2/26/03	Email attachment sent to request feedback on proposed changes. Phone call was also made.	Virginia Yoerg Regulatory Health Project Manager	1/24/03	203	General Correspondence

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
2/6/03	Status of S/N 196. Waiting for written response from FDA to our proposal to study oral Cremophor EL human exposure.	Virginia Yoerg, Regulatory Health Project Manager	12/13/02	196	General Correspondence – Request for FDA Feedback regarding proposal for the study of oral Cremophor EL human exposure
1/16/03	Pharm/Tox Teleconference - FDA will advise need for call next week.	Virginia Yoerg, Regulatory Health Project Manager	1/15/03 & 1/3/03	Agency Contact	Scheduling of Pharm/Tox teleconference
1/15/03	Pharm/Tox Teleconference – Still attempting to schedule telecon to discuss the Toxicology study of degradants	Virginia Yoerg, Regulatory Health Project Manager	1/3/03	Agency Contact	Scheduling of telecon
1/6/03	List of Attendees for EOP2 Clinical Meeting.	Nitin Patel, DAVDP, FDA	12/17/02	N/A	EOP2 Clinical meeting
1/3/03	Pharm/Tox Teleconference requested by FDA – Offered BI's availability for dates/times on either Jan. 6, 7 and 8.	Virginia Yoerg, Regulatory Health Project Manager	N/A	N/A	N/A
1/3/03	1/3/03 fax re: Microbiology comments SN 186-Phenotypic Assay.	Virginia Behr, DAVDP	11/15/02	186	Phenotypic Assay
12/30/02	Protocol for the Animal Safety Study in Dogs – If BIPI has urgency for review, contact Ms. Yoerg and send protocol via e-mail. Mr. Patel is out of office until Jan. 6, 2003.	Dr. Nitin Patel, Project Manager	12/13/02	Telecon	Protocol for Animal Safety in dogs

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DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
12/26/02	Pharm/Tox Teleconference requested during week of Jan. 6, 2003 to discuss the study of degradants.	Dr. Nitin Patel, Project Manager	N/A	N/A	N/A
12/18/02	CMC EOP 2 Meeting.	N/A	12/13/02	194	General Correspondence – Background Document for End of Phase 2 meeting
12/17/02	Clinical/Nonclinical End of Phase 2 meeting	Dr. Nitin Patel Project Manager	11/15/02	186	End of Phase 2 Meeting Package
12/13/02	FDA Contact Information for Dr. Gitterman.	Dr. Nitin Patel, Project Manager	N/A	N/A	N/A
12/12/02	Pharm/Tox Comments on 26 week Safety Tox Study and Teleconference.	Dr. Nitin Patel, Project Manager			FDA fax – Pharmacology/Toxicology comments in preparation for the 12/13/02 teleconference
12/11/02	RESIST II Protocol. Cancel telecon scheduled for today (12/11/02)	Dr. Nitin Patel, Project Manager	N/A	N/A	N/A
12/10/02	Ask about structure of degradation products specified in list of tests for drug product given in the EOP 2 package.	Dr. Boring, Chemistry Reviewer	12/13/02	194	General Correspondence – Background Document for End of Phase 2 meeting
12/10/02	Fax re: clinical and clinical pharmacology comments (EOP2)	Dr. Nitin Patel, Project Manager	11/15/02	186	General Correspondence- Background Document for End of Phase II Meeting

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
12/9/02	Outlines attendees and administrative details for Pharm/Tox Telecon scheduled for 12/11/02.	Dr. Nitin Patel, Project Manager	12/9/02	Agency Contact	Telecon schedule
12/9/02	EMail correspondence discussing Pharm/Tox telecon scheduled for 12/11/02.	Dr. Nitin Patel, Project Manager	N/A	N/A	N/A
12/4/02	EMail to FDA regarding 12/4/02 telecon – outlines status of BI minutes and includes word version of question list for EOP II Meeting.	Dr. Nitin Patel, Project Manager	11/22/02	Agency Contact	EMail from FDA with updated information on the 12/4/02 telecon
11/22/02	EMail from FDA with updated information on the 12/4/02 telecon.	Dr. Nitin Patel, Project Manager	N/A	N/A	N/A
11/21/02	Series of e-mails of correspondence involved with rescheduling the telecon to discuss PK/Tox Issue from SPA.	Dr. Nitin Patel, Project Manager	10/30/02	181	Response to FDA comments – FDA letters dated Aug 29, 2002(Special Protocol Assessment, ll82.12) and Sep 20, 2002 (ddI Drug Interaction)
11/19/02	Rescheduling of FDA 11/20/02 PK/Tox Telecon.	Dr. Nitin Patel, Project Manager	10/30/02	181	Response to FDA comments – FDA letters dated Aug 29, 2002(Special Protocol Assessment, ll82.12) and Sep 20, 2002 (ddI Drug Interaction)

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
11/8/02	FDA requests Telecon to discuss drug interaction portion of EOP 2 Package/FDA will send comments from 11/7 internal meeting.	Dr. Nitin Patel, Project Manager	10/30/02	181	Response to FDA comments – FDA letters dated Aug 29, 2002(Special Protocol Assessment, ll82.12) and Sep 20, 2002 (ddI Drug Interaction)
11/13/02	Clarify Issues regarding planning for TPV EOP 2 Meeting and Package.	Dr. Nitin Patel, Project Manager	10/30/02	181	Response to FDA comments – FDA letters dated Aug 29, 2002(Special Protocol Assessment, ll82.12) and Sep 20, 2002 (ddI Drug Interaction)
11/1/02	Mr. Patel requested 5 desk copies of Submission S/N 181 in preparation for a teleconference on 11/20/02.	Dr. Nitin Patel Project Manager	10/30/02	181	Response to FDA comments – FDA letters dated Aug 29, 2002(Special Protocol Assessment, ll82.12) and Sep 20, 2002 (ddI Drug Interaction)
10/23/02	Final Internal Meeting Minutes for Teleconference held on September 27 discussing Starting Materials in the Synthesis of TPV drug substance.		9/27/02	Telecon	Teleconference held on September 27, 2002
10/22/02	End of Phase 2 Meeting – Request for Dates Request for Teleconference on BI Responses to Special Protocol Assessment.	Dr. Nitin Patel Project Manager	10/11/02 10/15/02	177 Agency Contact	BI Telephone Contact referencing BI's October 11, 2002 letter EOP2 & F/U on Special Protocol Assessment telecon
10/15/02	Re: End of Phase 2 Meeting Request and Follow-Up/Special Protocol Assessment Follow-up Teleconference.	Dr. Nitin Patel, Project Manager	10/12/02	176	Request for Type B Meeting End of Phase II/Request for Teleconference Clinical/Pharmacokinetics

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
10/7/02, 10/16/02, 10/25/02	BI requested clarification of the minutes provided by FDA by email.	Dr. Nitin Patel, CSO Dr. Stephen Miller, Team Leader Dr. Dan Boring, Chemistry Reviewer	9/27/02	N/A	BI/FDA Teleconference – September 27th – FDA Minutes
9/27/02	To discuss the starting materials in the synthesis of Tipranavir drug substance.	Dr. Nitin Patel, CSO Dr. Steven Miller, Chemistry Team Leader Dr. Dan Boring, Reviewing Chemist	9/27/02	N/A	BI/FDA Teleconference –September 27th BI Minutes
9/18/02	Re: Tipranavir Special Protocol Assessment 1182.12 Follow-up.	Mr. Nitin Patel Project Manager	8/28/02 & 8/29/02 9/20/02	Agency Contact 161	TPV Special Protocol Assessment 1182.12 Request for Special Protocol Assessment – RESIST 1 Protocol 1182.12

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
8/30/02	To follow-up on setting a date for telecon to discuss starting material designation in the tipranavir drug substance synthesis.	Dr. Dan Boring Reviewing Chemist DAVDP	3/21/02 8/2/02 8/12/02 8/13/02	141 ACR ACR ACR	General Correspondence Starting materials BI notifying of fax sent with the information requested regarding proposal for 4 TPV as a starting material and to ask for confirmation of receipt. BI also followed-up on request for teleconference to discuss 4 TPV as a starting material.
8/28-8/29/02	TPV Special Protocol Assessment	Mr. Destry Sillivan, Project Manager Ms. Virginia Yoerg, Project Manager	7/18/02 7//19/02	161 ACR	Request for Special Protocol Assessment 1182.12 Request for desk copies of SPA
8/28/02	FDA can not approve Request for Special Protocol Assessment because submission did not meet requirements.	Mr. Destry Sillivan, Project Manager Ms. Virginia Yoerg, Project Manager	7/18/02 7/30-31/02	161 ACR	Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.12

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
8/2/02 8/12/02 8/13/02	BI notifying of fax sent with the information requested regarding proposal for 4 TPV as a starting material and to ask for confirmation of receipt. BI also followed-up on request for teleconference to discuss 4 TPV as a starting material.	Dan Boring DAVDP, FDA	6/17/02 3/21/02	N/A 141	Telephone contact – concurrence w/starting materials General Correspondence Starting materials
7/30/02-7/31/02	BI email FDA electronic version of Protocol 1182.12	Nitin Patel DAVDP, FDA	7/18/02	161	Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.12

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
7/30/02 7/23/02	FDA email with informal acceptance of ritonavir dose level to be used in rat carcinogenicity study and inquiry about dates of past IND Annual Reports	Nitin Patel DAVDP, FDA	7/19/02	162	Information Amendment-Pharmacology/Toxicology Reports Request for FDA Feedback/Teleconference – BI request concurrence with lowering dose level of ritonavir
			6/7/02 6/18/02 6/19/02 6/25/02 7/15/02 7/24/02 7/3/02	ACR ACR ACR ACR ACR ACR ACR	Request for Feedback on rat carcinogenicity study
7/24/02	FDA called to advise BI of faxed response from Pharm/Tox reviewers regarding acceptance of rat carcinogenicity dose levels and requested 3 additional desk copies of the Request for Special Protocol Assessment	Nitin Patel DAVDP, FDA	6/7/02 6/18/02 6/19/02 6/25/02	ACR ACR ACR ACR	Feedback on rat carcinogenicity study
			7/23/02	161	Telephone contact
			7/18/02	161	Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.12

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
7/22/02 7/19/02	FDA emailed with request for additional desk copies of Special Protocol Assessment	Nitin Patel DAVDP, FDA	7/18/02	161	Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.12
7/15/02	BI email FDA advising of a proposed decrease in RTV dose in the rat carcinogenicity study due to new Abbott data.	Nitin Patel DAVDP, FDA	5/24/02	151	Information Amendment: Pharmacology/Toxicology report and Request for FDA Feedback – BI seeking FDA concurrence with dose selection for the TPV/RTV and RTV groups for 2-year rat carcinogenicity study
7/3/02	BI email FDA inquiring about when to expect feedback on submissions regarding the need for ddI drug interaction study	Nitin Patel DAVDP, FDA	2/14/02	137	Information Amendment: Clinical/Request for Comment-Discontinuation of Tipranavir Study 1182.42

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
6/17/02	FDA called BI in regard to their review of BI's proposal regarding the starting materials	Dan Boring DAVDP, FDA	3/21/02 8/28/01 6/6/01 8/22/01 8/22/01	141 ACR 095 106 ACR	General Correspondence – BI seeking concurrence with designation of two starting materials in the synthesis of tipranavir drug substance Request for feedback on starting materials GC – starting materials GC – Definition of starting materials Starting Materials
6/7/02 6/18/02 6/19/02 6/25/02	BI emailed and phoned FDA about the need for FDA's feedback on the rat carcinogenicity study and the need for conducting another ddI drug interaction study. FDA faxed response to rat carcinogenicity study submissions but acknowledged that the other response was pending on the biopharm reviewer.	Nitin Patel DAVDP, FDA	2/14/02 5/24/02	137 151	Information Amendment: Clinical/Request for Comment-Discontinuation of Tipranavir Study 1182.42 Information Amendment: Pharmacology/Toxicology report and Request for FDA Feedback – BI seeking FDA concurrence with dose selection for the TPV/RTV and RTV groups for 2-year rat carcinogenicity study

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
5/24/02	BI emailed FDA seeking the status of FDA's feedback regarding need for ddI Drug Interaction study.	Nitin Patel DAVDP, FDA	2/14/02	137	Information Amendment: Clinical/Request for Comment-Discontinuation of Tipranavir Study 1182.42
5/02/02	FDA emailed BI asking for clarification in the amendments of the Investigator Brochure Changes	Nitin Patel DAVDP, FDA	4/26/02	146	Information Amendment – Clinical Investigators Brochure Version 5
3/7/02	BI called FDA to confirm receipt of submission that was faxed and to reiterate the request for feedback on the Phase II Protocol (1182.52)	Karen Young DAVDP, FDA	3/5/02	139	Response to FDA Request for Information
2/26/02	FDA informed BI of an internal attempts to set up teleconference with BI to discuss formulation and Pharmacology/Toxicology questions	Karen Young DAVDP, FDA	N/A	N/A	N/A
2/21/02	BI's minutes from teleconference between BI and FDA	Karen Young DAVDP, FDA & TPV Team	2/15/02	N/A	Fax from FDA Requesting Information from BI in order to address the clinical development program. FDA Requesting Chemistry, Pharmacology/Toxicology, Pharmacokinetics and Clinical information.

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
2/07/02	FDA called notifying BI that the Division will be having an internal meeting today to discuss the current status of TPV and what might be needed to support Phase III. FDA said they'd be sending pharmacokinetic, chemistry, pharm/tox and clinical comments in the next week.	Karen Young DAVDP, FDA	12/20/01 1/29/02	132 ACR	Information Amendment - Clinical Pharmacokinetics from 1182.6 DI Feedback
1/29/02	BI called FDA notifying them of the email of the submission on the tipranavir formulation, to inquire about the need for a teleconference and requesting feedback on the drug interaction program in support of Phase 3.	Karen Young DAVDP, FDA	12/20/01 1/29/02	132 ACR Contact	Information Amendment - Clinical Pharmacokinetics from 1182.6
1/29/02	FDA called requesting more information on SEDDS formulation used in clinical trials. BI responded saying that more information will be submitted either today or tomorrow.	Karen Young DAVDP, FDA	6/19/01	100	Information Amendment – CMC support for on-going and future clinical trails

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
1/28/02	FDA called to request additional information on the combination tox studies. BI asked FDA about data from 1182.6 study and requested comments on whether or not data was sufficient.	Karen Young DAVDP, FDA	12/27/01 12/20/01 9/25/01	133 132 ACR	Response to FDA Comments in regards to combination toxicology studies Information Amendment - Clinical Pharmacokinetics from 1182.6 Comment on 1182.6
12/13/01 12/18/01	BI called FDA to inform them that BI has suspended a study of TPV and ddI which was being conducted in Germany. BI ensured FDA that background information regarding this issue would be submitted shortly.	Karen Young DAVDP, FDA	N/A	N/A	Telephone contact
12/12/01 12/13/01	FDA called BI to • Advise project manager has changed for tipranavir • Discuss and request information on the SEDDS formulation	Karen Young DAVDP, FDA	N/A	N/A	Telephone contact
11/30/01	BI called FDA to check on the status of FDA's Meeting Minutes from Type C Meeting	Leslie Stevens DAVDP, FDA	10/5/01 11/7/01	N/A Agency Contact	Type C Meeting

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
11/15/01	BI called FDA to follow-up on status of BI's Request for Advice on Duration of Combination Toxicology Studies	Leslie Stephens Project Manager DAVDP	11/7/01	122	Request for Advice on Duration of Combination Toxicology Studies
11/07/01	BI called FDA to: • Advise Division of fax coming containing BI's proposal for combination toxicology studies • Advise Division that BI's meeting minutes from Type C meeting will also be faxed	Leslie Stephens Project Manager DAVDP	10/5/01	N/A	Type C Meeting
10/26/01	BI called FDA to: • Advise that BI plans on submitting a proposal for combination toxicology studies and request discussion of timing of submission, review and feedback of proposal • Follow-up on Division's offer to provide a draft template for genotyping and phenotyping	Leslie Stephens Project Manager DAVDP	10/5/01	N/A	Type C Meeting
9/26/01	BI called FDA to confirm extent of the background document that was needed electronically.	KarenYoung DAVDP, FDA	9/25/01	115	Desk Copies of General Correspondence - Background Document for Type C Meeting

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
9/25/01	FDA called to confirm internal meeting on 10/1/01 and give feedback on Protocol 1182.6	KarenYoung DAVDP, FDA	3/16/01	082	Response to FDA comments faxed on March 3 – 5, 2001 regarding 1182.6
9/24-25/01	FDA called questioning the eligibility criteria regarding how patients were assigned to the nucleosides/non-nucleosides and requested two additional copies of the background document	Leslie Stephens Project Manager DAVDP	1/19/01	076	Protocol Amendment – New Protocol and New Investigator for 1182.6
		KarenYoung DAVDP, FDA	9/25/01	115	Desk Copies of General Correspondence - Background Document for Type C Meeting
8/28/01	FDA informed BI of their response to the proposal for 5 TPV as a starting material in the synthesis of tipranavir drug substance. Bi asked for feedback on the original proposal.	Dan Boring DAVDP, FDA	6/6/01	095	General Correspondence – requesting FDA concurrence with designation of starting materials in the syntheses of tipranavir drug substance
			8/22/01	106	General Correspondence - Proposal for the definition of starting materials in synthesis of TPV drug substance
			7/18/01	N/A	ACR - FDA called BI regarding the proposal for starting materials

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
8/24/01	BI called FDA to confirm BI's availability for Type C meeting scheduled for October 5, 2001	Leslie Stephens Project Manager DAVDP	6/21/01	ACR	Meeting Plans
8/22/01	BI called FDA to: • Obtain status update on review of starting material proposal • Ask how FDA's new position on starting materials would be published • Obtain clarification on one of the existing (old) criteria for starting materials • Inquire about future CMC IND amendments	Dan Boring DAVDP, FDA	6/6/01 8/22/01	095 106	General Correspondence – requesting FDA concurrence with designation of starting materials in the syntheses of tipranavir drug substance General Correspondence - Proposal for the definition of starting materials in synthesis of TPV drug substance
7/18/01	FDA called BI regarding the proposal for starting materials	Dan Boring DAVDP, FDA	6/6/01	095	General Correspondence – requesting FDA concurrence with designation of starting materials in the syntheses of tipranavir drug substance
6/21/01	FDA called with date/time proposal for Type C Meeting teleconference.	Destry Sullivan DAVDP, FDA	6/20/02	Telecon	Telephone contact

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
6/20/01	FDA called in regards to BI's Type C Meeting Request. FDA wanted to propose a teleconference rather than a face-to-face meeting. BI explained reasoning for face-to-face meeting request and FDA said they'd get back to her on it. BI also inquired about feedback on safety update.	Destry Sullivan DAVDP, FDA	4/5/01	N/A	Pre-IND/End of Phase I Meeting
6/08/01	BI called FDA to: • Request a meeting in late July to discuss plans for the TPV pivotal program • Request feedback on availability of meeting minutes from April 5, 2001 • Request feedback on requested safety update	Anthony DeCicco DAVDP, FDA	4/5/01 4/3/01	N/A ACR	Pre-IND/End of Phase I Meeting Request for safety data & feedback on DI proposal
4/3/01	FDA called in regards to the upcoming pre-NDA Meeting. FDA requested that safety data be provided and that BI be ready to discuss drug interaction studies for tipranavir.	Leslie Stephens Project Manager DAVDP Joseph Toerner, DAVDP, FDA	N/A	N/A	Telephone contact

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
2/8/01	BI call FDA to confirm End of Phase I meeting date for April 5, 2001	Leslie Stephens Project Manager DAVDP	1/31/01 2/6/01 2/7/01	N/A N/A N/A	FDA requested change of date for the End of Phase 1 meeting date BI Request change to upcoming End of Phase 1 meeting date BI and FDA discuss potential meeting dates for Tipranavir End of Phase I meeting
2/7/01	BI and FDA discuss potential meeting dates for Tipranavir End of Phase I meeting	Leslie Stephens Project Manager DAVDP	1/31/01 2/6/01	N/A N/A	FDA requested change of date for the End of Phase 1 meeting date BI Request change to upcoming End of Phase 1 meeting date
2/6/01	BI Request change to upcoming End of Phase 1 meeting date	Leslie Stephens Project Manager DAVDP	1/31/01	N/A	FDA requested change of date for the End of Phase 1 meeting date
1/31/01	FDA requested change of date for the End of Phase 1 meeting date	Leslie Stephens Project Manager DAVDP	N/A	N/A	N/A
1/15/01	BI called to confirm BI's meeting date of 3/1/01.	Leslie Stephens Project Manager DAVDP	N/A	N/A	N/A

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
9/16/99	FDA called with questions regarding Protocol M/3342/0006. PNU ensured they would look into them and get back as soon as possible.	Leslie Stevens DAVDP, FDA	8/20/99	053	Protocol Amendment – Change in Protocol M/3342/0006 Amendment 2
5/3/99	PNU called to clarify if submitting 16 weeks data for naïve patients instead of 24 weeks when filing the NDA for accelerated approval would be acceptable. FDA said they would have to wait until the Phase II studies are complete to see what the data looks like.	Christine Kelly DAVDP, FDA	9/98	N/A	Telephone contact
4/6/99	FDA called to inform PNU that protocols (13 and 19) were missing from SN 043. PNU told FDA that they would resubmit SN 043.	Christine Kelly Joe Toerner DAVDP, FDA	3/29/04	043	Protocol Amendment – • New Protocol M/3342/0013 • Change in Protocol M/3342/0006 Amendment 1 • New Investigators for Protocol M/3342/0006
3/29/99	FDA called to remind PNU that 26-week rat and 39-week dog reports. Were due by April 2, 1999 or clinical study M/3342/0006 would be put on clinical hold.	Christine Kelly Joe Toerner DAVDP, FDA	3/24/99	040 041	FDA Request for information – Clinical Comments on SN 040 and SN 041
3/24/99-3/23/99	Call made regarding request for animal toxicology reports.	Christine Kelly DAVDP, FDA	3/24/99	040 041	FDA Request for information – Clinical Comments on SN 040 and SN 041

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TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
9/22/98	PNU notified the FDA about a minor error on cover sheet on Protocol M/3342/0011. "Final" protocol should have been stated rather than "Draft". FDA asked for new cover page be sent.	David Staten DAVDP, FDA	9/23/98	032	Protocol Amendment –New Protocol M/3342/0011 – Draft Information Amendment – CMC data including new SEDDs formulations and Toxicology Report a0014475
9/21/98	FDA called notifying PNU that "boiler plate" investigational drug statement was missing from final labels that were being used in studies. PNU ensured correction to be sent.	Debra Gump DAVDP, FDA	3/18/98	021	Information Amendment – CMC information on the synthesis of drug substance, new formulation, draft labeling, and changed storage condition for 150 mg capsules
9/8/98	FDA called to reschedule Sept 9 teleconference due to conflict in attendee's schedule. PNU decided to proceed without that individual. FDA request more information on the subject of discussion.	Debra Gump DAVDP, FDA	N/A	N/A	N/A
8/21/98	Contact regarding the background document for the September 8th teleconference between PNU and FDA	Debra Gump DAVDP, FDA	N/A	N/A	N/A

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
7/29/98	PNU call FDA to confirm September 9th is ok with the PNU team for the teleconference to discuss further development plans for tipranavir. PNU promises background information to be sent shortly.	Debra Gump DAVDP, FDA	7/28/98	N/A	Telephone contact
7/28/98	PNU call FDA to confirm September date for teleconference to discuss further development plans for tipranavir. FDA offered a Sept. 9 date.	Debra Gump DAVDP, FDA	N/A	N/A	N/A
6/17/98	FDA approved changes to Protocol M/3342/0004 that were previously faxed to her	Debra Gump DAVDP, FDA	6/10/98 6/2/98	N/A 025	PNU fax containing proposed changes to Protocol M/3342/0004 Protocol Amendment – Change in Protocol M/3342/004 Amendment 8 Amendment A, 6 and 7

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
6/11/98	Called FDA to confirm receipt of fax with proposed amendment to Protocol M/3342/004	Debra Gump DAVDP, FDA	6/2/98	025	Protocol Amendment – Change in Protocol M/3342/004 Amendment 8
2/17/98	FDA relayed message that protocol M/3342/0004 (Amendment 9) were ok with Division.				
2/11/98	Call placed to FDA to confirm fax of proposed amendment to Protocol M3342/0004. It was confirmed.				
9/10/97	Inform FDA of plans of submitting 3-month interim reports for each 6-month animal study	Kimberly A. Struble DAVDP, FDA	6/5/97 5/15/97 4/15/97	N/A N/A 006	Telephone contact Request for feedback to the strategy of conducting 6-month instead of 3-month toxicity study Information Amendment: Pharmacology/ Toxicology - Update to Gantt chart of proposed clinical trails together with one for proposed preclinical studies designed to support the safety, Final Toxicology Reports
6/5/97	FDA Request to prepare to submit for	Kimberly A.	5/15/97	N/A	Request for feedback to the strategy

TIPRANAVIR AGENCY CONTACT REPORT STATUS SHEET

DATE	REASON FOR CONTACT	NAME OF CONTACT PERSON	Date of Reference	Serial No. of Reference	Description of Reference
	each 6 month animal study a 6 month interim report	Struble DAVDP, FDA	4/15/97	006	of conducting 6-month instead of 3-month toxicity study Information Amendment: Pharmacology/ Toxicology - Update to Gantt chart of proposed clinical trails together with one for proposed preclinical studies designed to support the safety, Final Toxicology Reports
6/6/96	PN&U requested FDA opinion on dose level selection for the 30 day dog study for tipranavir. FDA agreed on the 320 mg/kg/day.	Kimberly A. Struble DAVDP, FDA	N/A	N/A	N/A
11/20/96	IND assigned 51-979	Dawn M. Roberts	N/A	N/A	References for IND for PNU-140690
12/16/96	FDA telephone contact on 12/13/96 concerning PNU-140690 for AIDS, AIDS related complex and treatment of Asymptomatic HIV Positives RESCRIPTOR Tablets	Dawn M. Roberts	N/A	N/A	December 13, 1996 Safety Review meeting - FDA determined it is safe for P&U to proceed with the single oral dose escalation study in healthy volunteers (protocol M/3342/0001)
12/13/96	FDA determined it was safe for P&U to proceed with the single oral dose escalation study in healthy volunteers. (Protocol M/3342/0001)	Kimberly A. Struble DAVDP, FDA	12/13/96	001	Protocol Amendment - Change in Protocol M/3342/001 - Amendment 1

Tipranavir Serial Number Log

Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
000	• Original IND Application	11/13/96	N/A	N/A	
001	• Protocol Amendment - Change in Protocol M/3342/001 - Amendment 1 • IRB Letter of Approval and Patient Consent Form for evidence of approval of Protocol M/3342/0001 by the Bronson Methodist Hospital Human Use Committee	12/13/96	000	Original Protocol	11/13/96
002	• Protocol Amendment – Change in Protocol M/3342/001 Amendment 2	1/7/97	000 001	Original Protocol Amendment 1 to M/3342/0021	11/13/96 12/13/96
003	• Protocol Amendment - New Protocol M/3342/002 (CMC and labeling information) • Information Amendment - Toxicology Report	1/2/97	N/A	N/A	N/A
004	• General Correspondence - Response to FDA faxes containing Clinical, Pharmacology, Microbiology, and Chemistry comments	1/31/97	N/A	FDA faxes	12/17/96 12/19/96

Tipranavir Serial Number Log

Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
005	• Protocol Amendment - Change in Protocol M/3342/002 Amendment 1 • Information Amendment - Toxicology Reports • Correction to General Correspondence - SN 004 submitted 1/31/97	2/20/97	001	Original Protocol	12/13/96
006	• Information Amendment: Pharmacology/ Toxicology - Update to Gantt chart of proposed clinical trails together with one for proposed preclinical studies designed to support the safety • Final Toxicology Reports,	4/15/97	004 000	Gantt chart submitted Draft Toxicology reports	1/31/97 11/13/96
007	• Information Amendment: Toxicology Report	5/7/97	N/A	N/A	N/A

008	• Protocol Amendment – New Protocol M/3342/0003 and New Investigator, Dr. Dennis W. Schneck
	• Information Amendment –
	  • CMC
	  • Updated stability data
	  • Labeling for Protocol M/33420003
		5/9/97	N/A	N/A	N/A

009	• Protocol Amendment – • New Protocol and Investigator for M/3342/0005	7/3/97	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	• Information Amendment – Labeling for M/3342/0005				
010	• Protocol Amendment – New Protocol M/3342/004	7/10/97	N/A	N/A	N/A

011	• Protocol Amendment – New Investigator, for M/3342/004
	• Information Amendment -
	  • CMC information in support of the trial product
	  • Labeling for M/3343/004
		8/4/97	010	Original protocol	7/10/97

012	• Protocol Amendment – Change in Protocol M/3342/0004 Amendment 1 • Information Amendment – Toxicology/Pharmacology Reports	8/22/97	010	Original Protocol	7/10/97
013	• Information Amendment – Toxicology Support for Protocol M/3342/0004.	8/27/97	010	Original Protocol	7/10/97
014	• General Correspondence – P&U Minutes of Teleconference that discussed P&U's proposal to extend the ongoing 26-week non-rodent toxicology study to 39 weeks	9/25/97	N/A	Teleconference between P&U and FDA on September 22, 1997	9/22/97
015	• Protocol Amendment – Change in Protocol M/3342/0004 – Amendment 2 and 3 • Info Amend – Tox.Rep, TR 7228-97-052	10/10/97	010 012	Original Amendment 1	7/10/97 8/22/97

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016	• Protocol Amendment – New Protocol and Investigator for M/3342/0007 • Information Amendment – CMC information and labeling in support of M/3342/0007	10/24/97	N/A	N/A	N/A
017	• Protocol Amendment – New Protocol and Investigator for M/3342/008 • Amendment of IND to reflect proposal to discontinue the routine performance of thyroid function testing in new clinical trials with PNU-140690 • Information Amendment – • Labeling for M/3342/0008 • Pharmacology /Toxicology Reports	12/23/97	 N/A N/A	 Fax sent to FDA with discontinue the routine performance of thyroid function testing in new clinical trials on 11/10/97 Approval of proposal communication by FDA	 11/10/97 11/14/97
018	• Protocol Amendment – • New Protocol DRAFT M/3342/0009 Change in Protocol – M/3342/0004 Amendments 4 and 5 • M/3342/0008 Amendments 1	2/4/98	 N/A 010 012 015 017	 N/A Original Protocol Amendment 1 Amendments 2 and 3 Original Protocol	 N/A 7/10/97 8/22/97 10/10/97 12/23/97

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	and 2 • New Investigator for M/3342/0004 • Information Amendment: Pharmacology and ADME Reports		010 012 015	Original Protocol Amendments 1 Amendments 2 and 3	7/10/97 8/22/97 10/10/97
019	• IND Annual Report - reporting period through 9/30/97	2/6/98	N/A	N/A	N/A
020	• Protocol Amendment – FINAL Protocol and New Investigator M/3342/0009 • Labeling in support of Protocol M/3342/0009 • Information Amendment – Pharmacology/Toxicology	2/25/98	018	Draft Protocol M/3342/0009	2/4/98
021	• Information Amendment – CMC information on the synthesis of drug substance, new formulation, draft labeling, and changed storage condition for 150 mg capsules	3/18/98	008	Information Amendment – CMC	5/9/97

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
022	• Protocol Amendment – Change in Protocol M/3342/0004 Amendments A, 6, and 7	4/1/98	010 012 015 018	Original Protocol Amendment 1 Amendment 2 and 3 Amendment 4 and 5	7/10/97 8/22/97 9/30/97 2/4/98
023	• Protocol Amendment – Change in Protocol M/3342/0009 Amendment 1	4/30/98	018 020	Draft protocol Final Original Protocol	2/4/98 2/25/98
024	• Protocol Amendment – New Investigators for Protocol M/3342/0004	5/21/98	010 012 015 018 022	Original Protocol Amendment 1 Amendment 2 and 3 Amendment 4 and 5 Amendment 6 and 7	7/10/97 8/22/97 9/30/97 2/4/98 4/1/98
025	• Protocol Amendment – Change in Protocol M/3342/004 Amendment 8	6/2/98	010 012 015 018 022	Original Protocol Amendment 1 Amendment 2 and 3 Amendment 4 and 5 Amendment 6 and 7	7/10/97 8/22/97 9/30/97 2/4/98 4/1/98
026	• General Correspondence – Meeting Request to review BI's pharmacokinetic, efficacy and safety data	7/13/98	N/A	N/A	N/A
027	• Protocol Amendment – Change in Protocol M/3342/0004 Amendment 9	7/30/98	010 012 015	Original Protocol Amendment 1 Amendment 2 and 3	7/10/97 8/22/97 9/30/97

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			018 022 025	Amendment 4 and 5 Amendment 6 and 7 Amendment 8	2/4/98 4/1/98 6/2/98
028	• Protocol Amendment – New protocol M/3342/0012	8/25/98	N/A	N/A	N/A
029	• General Correspondence – Teleconference Background Package for September 9, 1998 teleconference to discuss BI's pharmacokinetic, efficacy and safety data	8/26/98	026	General Correspondence – Meeting Request	7/13/98
030	• General Correspondence – Teleconference Meeting Minutes from September 9, 1998 teleconference discussing BI's pharmacokinetic, efficacy and safety data	9/18/98	026 029 N/A	General Correspondence – Meeting Request General Correspondence – Teleconference Background Package Teleconference between BI and FDA	7/13/98 8/26/98 9/9/98
031	• Information Amendment – Clinical Study Report and Toxicology Report	9/21/98	N/A	N/A	N/A
032	• Protocol Amendment –New Protocol M/3342/0011 – Draft • Information Amendment – CMC data	9/23/98	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	including new SEDDs formulations and Toxicology Report a0014475				
033	• General Correspondence – Update to Serial No. 021, new labeling		N/A 021	Telephone call between BI and FDA Information Amendment	9/21/98 3/18/98
034	• General Correspondence –Correction to Serial No. 032 - Final Protocol M/3342/0011	10/5/98	N/A 032	Telephone call between BI and FDA Protocol Amendment –New Protocol M/3342/0011 – Draft	9/22/98 9/23/98
035	• General Correspondence – Response to FDA Fax – Biopharmaceutics Comments on Protocol M/3342/0012	10/6/98	028	FDA Fax with Biopharmaceutics comments	9/23/98
036	• Protocol Amendment – Change in Protocol M/3342/0012 Amendment 1	10/22/98	028	Original Protocol	825/98

037	• Protocol Amendment
	  • New Protocol and Investigator for M/3342/0014
	• Information Amendment
	  • Clinical Analysis Memo
		11/2/98	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	• Clinical Study Reports • CMC labeling for M/3342/0004 • Pharmacology/Toxicology Reports				
038	• Information Amendment – Pharmacology/Toxicology Reports	12/4/98	N/A	N/A	N/A
039	• Protocol Amendment – • New Protocol – M/3342/0115 • Changes in Protocol M/3342/0004 Amendment 10 • Amendment to Clinical Study Report a0024338	12/9/98	 010 012 015 018 022 025 027 037	 Original Protocol Amendment 1 Amendment 2 and 3 Amendment 4 and 5 Amendment 6 and 7 Amendment 8 Amendment 9 Final Trial Report M/3342/0007	 7/10/97 8/22/97 9/30/97 2/4/98 4/1/98 6/2/98 7/30/98 11/23/98
040	• Annual Report – Reporting Period 10/1/97 – 9/30-98	1/29/99	N/A	N/A	N/A
041	• Protocol Amendment – New Protocol M3342/0006	2/5/99	N/A	N/A	N/A
042	• Protocol Amendment – New Investigators for M/3342/0015	3/1/99	039	Original Protocol	12/9/98

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
043	• Protocol Amendment – • New Protocol M/3342/0013 • Change in Protocol M/3342/0006 Amendment 1 • New Investigators for Protocol M/3342/0006	3/29/99	041	Original Protocol	2/5/99
044	• Information Amendment – CMC, updated sections of drug protocol	3/31/99	000	Original IND Application	11/13/96
045	• Protocol Amendment – Toxicology Study Reports	4/1/99	N/A	N/A	N/A
046	• General Correspondence – Response to FDA Questions regarding Submissions SN 040 and 041	4/2/99		FDA Fax	3/24/99
			040	Annual Report – Reporting Period 10/1/97 – 9/30-98	1/29/99
			041	Annual Report – Reporting Period 10/1/97 – 9/30-98	2/5/99
047	• Protocol Amendment – Toxicology Study Report resubmission	4/5/99	045	Protocol Amendment – Toxicology Study Reports a0011536	4/1/99
048	• General Correspondence – Request for Review of Carcinogenicity Study Protocol	4/6/99	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
049	• Protocol Amendment – • New Protocol M/3342/0016 • New Investigator for Protocol M/3342/0006 • New Investigator for Protocol M/3342/0013 • New Investigator for Protocol 69INF0013-019 • Change in Investigator for Protocol M/3342/0015	5/10/99	 041 043 043 043 039	 Original Protocol Amendment 1 Original Protocol Original Protocol Original Protocol	 2/5/99 3/29/99 3/29/99 3/29/99 12/9/98
050	• Protocol Amendment – • New Investigator for Protocol M/3342/0006 • Information Amendment –Toxicology Data	5/27/99	 041 043 N/A	 Original Protocol Amendment 1 N/A	 2/5/99 3/29/99 N/A
051	• Protocol Amendment – New Investigators for Protocol M/3342/0006	6/25/99	041 043	Original Protocol Amendment 1	2/5/99 3/29/99
052	• Protocol Amendment – New Investigators for M/3342/0006	8/9/99	041 043	Original Protocol Amendment 1	2/5/99 3/29/99

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	• Information Amendment – Pharmacology/Toxicology Data –		N/A	N/A	N/A
053	• Protocol Amendment – Change in protocol M/3342/0006 Amendment 2	8/20/99	041 043	Original Protocol Amendment 1	2/5/99 3/29/99
054	• Protocol Amendment – • Change in Protocol M/3342/0016 – Amendment 1 • New Investigator M/3342/0006 • Added sub-investigators M/3342/0006 • Information Amendment – Clinical Data a0038615	9/21/99	049 041 043 053 020	Original protocol Original Protocol Amendment 1 Amendment 2 Original Protocol	5/10/99 2/5/99 3/29/99 8/20/99 2/24/98
055	• Desk Copy of Serial No. 044	9/24/99	044	Information Amendment – CMC updated sections of drug protocol	4/7/99
056	• Desk copy of Serial No. 040	9/30/99	045	Annual Report – Reporting Period 10/1/97 – 9/30-98	1/29/99
057	• Protocol Amendment – New investigator and added sub-investigator for M/3342/0006 • Info Amend – Pharm Data a0056253	10/21/99	041 043 053	Original Protocol Amendment 1 Amendment 2	2/5/99 3/29/99 8/20/99

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
058	• Information Amendment – Pharmacology/Toxicology Data	10/27/99	N/A	N/A	N/A
059	• Protocol Amendment – Change in Protocol M/3342/0004 Amendment 11	11/23/99	010 012 015 018 022 025 027 039	Original Protocol Amendment 1 Amendment 2 and 3 Amendment 4 and 5 Amendment A, 6 and 7 Amendment 8 Amendment 9 Amendment 10	7/10/97 8/22/97 9/30/97 2/4/98 4/1/98 6/2/98 7/30/98 12/9/98
060	• Protocol Amendment – • New Investigators and new laboratory to M/3342/0016 • New sub-investigators for Protocol M/3342/0006 • Information Amendment – Pharmacology/Toxicology Data	12/22/99	049 041 043 053 N/A	Original protocol Original Protocol Amendment 1 Amendment 2 N/A	5/10/99 2/5/99 3/29/99 8/20/99 N/A
061	• Protocol Amendment – Clinical Study Reports • a0063183 (Protocol M/3342/0001) • a0062071 (protocol M/3342/0011)	12/29/99	000 001 002 034	Original Protocol Amendment 1 Amendment 2 Final Protocol	11/13/96 12/12/96 1/7/97 10/5/98

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
062	• Protocol Amendment – Clinical Study Report and New Investigators to Protocol M/3342/0016	1/18/00	049 054	Original protocol Amendment 1	5/10/99 9/21/99
063	• Annual Report – October 1, 1998 – September 30, 1999	2/15/00	N/A	N/A	N/A
064	• Protocol Amendment – New Investigators for M/3342/0016 • Information Amendment – Toxicology Reports	2/18/00	049 054 N/A	Original protocol Amendment 1 N/A	5/10/99 9/21/99 N/A
065	• Protocol Amendment – New Investigators new sub-investigators and new satellite for Protocol M/3342/0016 • Information Amendment – • Clinical Report • Toxicology Report	3/17/00	049 054 N/A	Original protocol Amendment 1 N/A	5/10/99 9/21/99 N/A
066	• Protocol Amendment – Change in Protocol M/3342/0006 Amendment 3	3/21/00	041 043 053	Original Protocol Amendment 1 Amendment 2	2/5/99 3/29/99 8/20/99
067	• Protocol Amendment – New Investigators and sub-investigators for Protocol M/3342/0016 • Information Amendment – Toxic reports	4/18/00	049 054 N/A	Original protocol Amendment 1 N/A	5/10/99 9/21/99 N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
068	• General Correspondence – Transfer of Sponsorship from Pharmacia & Upjohn Company to Boehringer Ingelheim Pharmaceuticals, Inc.	4/19/00	N/A	N/A	N/A
069	• General Correspondence – Boehringer Ingelheim's acknowledgment of transfer of IND Sponsorship	4/19/00	068	Pharmacia & Upjohn's General Correspondence – Transfer of Sponsorship	4/19/00
070	• Protocol Amendment – New Investigator for M/3342/0016 • Information Amendments – CMC and Pharmacology/Toxicology Data	5/30/00	049 054 N/A	Original protocol Amendment 1 N/A	5/10/99 9/21/99 N/A
071	• Protocol Amendment – Change in Protocol M/3342/0004 (BI Trial 1182.1) Amendment 12	8/3/00	010 012 015 018 022 025 027 039 059	Original Protocol Amendment 1 Amendment 2 and 3 Amendment 4 and 5 Amendment 6 and 7 Amendment 8 Amendment 9 Amendment 10 Amendment 11	7/10/97 8/22/97 9/30/97 2/4/98 4/1/98 6/2/98 7/30/98 12/9/98 11/23/99
072	• Protocol Amend – New Protocol 1182.5	9/13/00	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
073	• Protocol Amendment – New Investigators for: • 1182.5 • 1182.1 (M/3342/0004) • Updated FDA Form 1572 for Investigator in BI Trial 1182.7 (M/3342/0016)	10/9/00	 072 010 049 054	 Original Protocol Original Protocol (1182.1) Original protocol Amendment 1	 9/13/00 7/10/97 5/10/99 9/21/99
074	• Response to FDA Comments dated September 13, 2000 which contained comments by the Medial Reviewer and Medical Team Leader regarding Protocol Amendment – Change in Protocol M/3342/0004/BI Trial 1182.1	11/6/00	N/A 071	Fax from FDA Protocol Amendment – Change in Protocol M/3342/0004/BI Trial 1182.1	9/13/00 8/3/00
075	• Request for Type B Meeting to discuss clinical development plans for tipranavir	12/27/00	N/A	Teleconference with FDA	12/21/00
076	• Protocol Amendment – New Protocol and New Investigator for 1182.6	1/19/01	N/A	N/A	N/A
077	• General Correspondence – Background Document for End of Phase I Meeting scheduled for 4/5/01	2/9/01	075 N/A	Request for Type B Meeting DAVDP Advisory Committee Meeting	12/27/00 1/11/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
078	• Protocol Amendment – • New protocol for 1182.17 • Change in Protocol 1182.4 Amendment 2 • Change in Protocol 1182.6 - Amendment 1	2/12/01	N/A 049 054 076	N/A Original protocol Amendment 1 Original protocol	N/A 5/10/99 9/21/99 1/19/01
079	• Annual Report – October 1, 1999 – September 30, 2000	2/13/01	N/A	N/A	N/A
080	• Protocol Amendment – Change in Protocol 1182.6 Amendment 2	2/23/01	049 054	Original protocol Amendment 1	5/10/99 9/21/99
081	• Information Amendment – Clinical Trial Reports	3/7/01	N/A	N/A	N/A
082	• Response to FDA comments faxed on March 3 – 5, 2001 regarding 1182.6	3/16/01	N/A 076 077	Fax with FDA Comments regarding 1182.6 Original Protocol End of Phase I Background Document	3/1 and 5/01 1/19/01 2/9/01
083	• General Correspondence – Update to Background Document for End of Phase I Meeting scheduled for April 5, 2001	3/30/01	077 N/A	End of Phase I Background Document Telephone conservation between BIPI and FDA	2/9/01 3/29/01

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084	• Response to FDA Comments regarding BI Trial No. 1182.5	4/3/01	072	Fax with FDA Comments regarding 1182.5	11/9/00
085	• Response to FDA Comments regarding BI Trial No. 182.17	4/3/01	078	Fax with FDA Comments regarding 1182.17	3/19/01
086	• Information Amendment – Clinical Trial Report	4/4/01	N/A	N/A	N/A
087	• Response to FDA Comments regarding BI's upcoming Pre-IND meeting	4/4/01	N/A	Telephone conversation between BIPI and FDA regarding upcoming pre-IND meeting	4/3/01
088	• General Correspondence – Meeting Minutes from End of Phase I Meeting	4/19/01	N/A	End of phase I Meeting	4/5/01
089	• IND Safety Report – • Initial Report 2001-BP-01258	4/24/01	N/A	N/A	N/A
090	• Protocol Amendment – New Investigators for:	5/7/01			
	• 1182.2		041	Original Protocol	2/5/99
			043	Amendment 1	3/29/99
			053	Amendment 2	8/20/99
			066	Amendment 4	3/21/00
	• 1182.6		076	Original Protocol	1/19/01
			078	Amendment 1	2/12/01
			080	Amendment 2	2/23/01
	• 1182.17		078	Original Protocol	2/12/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
091	• IND Safety Report • Initial 2001-BP-01439	5/10/01	N/A	N/A	N/A
092	• IND Safety Report • Initial Report 2001-BP-01639 • Follow-up #1 2001-BP-01439	5/25/01	 N/A 091	 N/A Initial Report	 N/A 5/10/01
093	• IND Safety Report Initial 2001-DE05034	5/29/01	N/A	N/A	N/A
094	• Protocol Amendment – Changes in protocol • 1182.2 Amendment 4 • 1182.4 Amendment 3	5/31/01	 041 043 053 066 049 054 078	 Original Protocol Amendment 1 Amendment 2 Amendment 3 Original Protocol Amendment 1 Amendment 2	 2/5/99 3/29/99 8/20/99 3/21/00 5/10/99 9/21/99 2/12/00
095	• General Correspondence – requesting FDA concurrence with designation of starting materials in the syntheses of tipranavir drug substance	6/6/01	N/A	N/A	N/A
096	• Protocol Amendment – New Investigators for: • 1182.6		 076 078	 Original Protocol Amendment 1	 1/19/01 2/12/01

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			080	Amendment 2	2/23/01
	• 1182.17		078	Original Protocol	2/12/01
097	• IND Safety Report –	6/12/01	091	Initial Report	5/10/01
	• Follow-up #2 2001-BP-01439		092	Follow-up #`1	5/25/01
098	• IND Safety Report –	6/12/01	092	Initial Report	5/25/01
	• Follow-up #1 2001-BP-01639				
099	• Request for Type C Meeting to discuss clinical development plans	6/14/01	N/A	End of phase I Meeting with DAVDP	4/5/01
			088	Draft Meeting minutes from End of Phase I Meeting	4/19/01
			N/A	Telephone conversation between BIPI and FDA	6/8/01
100	• Information Amendment – CMC support for on-going and future clinical trails	6/19/01	N/A	N/A	N/A
101	• Protocol Amendment – Changes in 1182.17 Amendment 1	6/25/01	078	Original Protocol	2/12/01
102	• IND Safety Reports	7/3/01			
	• Initial Report 2001-FF-C0384		N/A	N/A	N/A
	• Follow-up Report #3 2001-BP-01439		091	Initial Report	5/10/01
			092	Follow-up #1	5/25/01
			097	Follow-up #2	6/12/01
	• Follow-up Report #2 2001-BP-01639		092	Initial Report	5/25/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			098	Follow-up #1	6/12/01
103	• IND Safety Report Initial Report 2001- DB-00029	7/25/01	N/A	N/A	N/A
104	• Protocol Amendment - New Investigators • 1182.6 • 1182.17	7/27/01	 076 078 080 078 101	 Original Protocol Amendment 1 Amendment 2 Original Protocol Amendment 1	 1/19/01 2/12/01 2/23/01 2/2/01 6/25/01
105	• IND Safety Report • Follow-up # 1 2001-DE-05034	8/1/01	093	Initial Report	5/29/01
106	• General Correspondence - Proposal for the definition of starting materials in synthesis of TPV drug substance	8/3/01	095 N/A	General Correspondence – requesting FDA concurrence with designation of starting materials in the syntheses of tipranavir drug substance Teleconference between FDA and BI	6/6/01 7/18/01
107	• IND Safety Report • Follow-up Report #1 2001-DB-00029	8/8/01	103	Initial Report	7/25/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
108	• IND Safety Reports • Follow-Up Report #4 2001-BP-01439 • Follow-Up Report #3 2001-BP-0639	8/14/01	 091 092 097 102 092 098 102	 Initial Report Follow-up #1 Follow-up #2 Follow-up #3 Initial Report Follow-up # 1 Follow-up # 2	 5/10/01 5/25/01 6/12/01 7/3/01 5/25/01 6/12/01 7/3/01
109	• Request for Type C Meeting - Requesting FDA feedback on adequacy of our dose selection approach.	8/17/01	N/A 088	End of Phase I Meeting End of Phase I Meeting Minutes	4/5/01 4/19/01
110	• IND Safety Report • Follow-up Report #2 2001-DB-00029	8/20/01	103 107	Initial Report Follow-up #1	7/25/01 8/8/01
111	• Protocol Amendment - Changes in Protocol 1182.6 Amendment 3	8/20/01	076 078 080	Original Protocol Amendment 1 Amendment 2	1/19/01 2/12/01 2/23/01
112	• IND Safety Report • Follow-up Report #1 2001-FF-C0384	8/27/01	102	Initial Report	7/3/01
113	• Protocol Amendment - New Investigators for 1182.17	8/29/01	078 101	Original Amendment 1	2/12/01 6/25/01
114	• IND Safety Reports • Follow-up Report #5 2001-BP-01439	8/30/01	091 092 097 102	Initial Report Follow-up #1 Follow-up #2 Follow-up #3	5/10/01 5/25/01 6/12/01 7/3/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			108	Follow-up #4	8/14/01
115	• Desk Copies of General Correspondence - Background Document for Type C Meeting	9/25/01	109	General Correspondence - Background Document for Type C Meeting	8/17/01
116	• Response to FDA Request for Information – Diskette with MS Word Files from Background Document for Type C Meeting	9/26/01	109 115	General Correspondence - Background Document for Type C Meeting General Correspondence - Background Document for Type C Meeting	8/17/01 9/25/01
117	• Response to FDA Request for Information containing a chart with the Overview of Tipranavir Clinical Trial Program with Particular Focus on Subjects 1182.12 and 1182.48	9/27/01	N/A	N/A	N/A
118	• IND Safety Reports • Follow-up Report #4 2001-BP-01639	9/28/01	092 098 102 108	Initial Report Follow-up # 1 Follow-up # 2 Follow-up # 3	5/25/01 6/12/01 7/3/01 8/14/01
119	• IND Safety Report • Initial Report 2001-FF-C0647	10/15/01	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
120	• Information Amendment - Pharmacology/Toxicology	10/15/01	N/A	N/A	N/A
121	• Protocol Amendment	10/30/01			
	• New Protocols 1182.37 and 1182.41		N/A	N/A	N/A
	• Changes in Protocol 1182.37 Amendment 1		N/A	N/A	N/A
	• New Investigators for 1182.6		076 078 080 111	Original Protocol Amendment 1 Amendment 2 Amendment 3	1/19/01 2/12/01 2/23/01 8/20/01
	• New Investigators for 1182.17		078 101	Original Amendment 1	2/12/01 6/25/01
122	• General Correspondence - Request for Advice on Duration of Combination Toxicology Studies	11/7/01	N/A	N/A	N/A
123	• General Correspondence - Meeting Minutes from October 5, 2001 meeting discussing BI's clinical Development plans and Interaction Program	11/7/01	N/A	FDA and BI Meeting	10/5/01
124	• IND Safety Report • Follow-up Report #5 2001-BP-01639	11/8/01	092 098 102 108 118	Initial Report Follow-up # 1 Follow-up # 2 Follow-up # 3 Follow-up # 4	5/25/01 6/12/01 7/3/01 8/14/01 9/28/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
125	• Protocol Amendment – Changes in Protocol • 1182.37 Amendment 2 • 1182.41 Amendment 1 • Information Amendment - Clinical Report, Tipranavir Investigators Brochure	11/13/01	 121 121	 Original Protocol and Amendment 1 Original Protocol	 10/30/01 10/30/01
126	• Response to FDA Request for Information in regards to fax requesting sample patient informed consent form and investigators documentation for Protocols 1182.37 and 1182.41	11/20/01	N/A 121 125 121 125	Fax from FDA Amendment 1 (1182.37) Amendment 2 (1182.37) Original Protocol (1182.41) Amendment 1 (1182.41)	11/16/01 10/30/01 11/13/01 10/30/01 11/13/01
127	• Serial Number Correction to Information Amendment – Clinical/Clinical Pharmacokinetics	12/4/01	N/A	Information Amendment – Clinical/Clinical Pharmacokinetics	11/30/01
128	• IND Annual Report – Reporting period October 1, 2000 – September 28, 2001	12/14/01	N/A	N/A	N/A
129	• General Correspondence – Discontinuation of Tipranavir Study 1182.42	12/19/01	N/A	Telephone conversation between BI and FDA	12/18/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
130	• Protocol Amendment - Changes in Protocol 1182.37 Amendment 3	12/19/01	121 121 125	Original Protocol Amendment 1 Amendment 2	10/30/01 10/30/01 11/13/01
131	• IND Safety Report Follow-up #2 2001-DE-05034(2)	12/20/01	093 105	Initial Report Follow-up #1	5/29/01 8/1/01
132	• Information Amendment - Clinical Pharmacokinetics from 1182.6	12/20/01	N/A 076 078 080 111	Clinical Development Meeting between BI and FDA Original Protocol Amendment 1 Amendment 2 Amendment 3	10/5/01 1/19/01 2/12/01 2/23/01 8/20/01
133	• Response to FDA Comments in regards to combination toxicology studies	12/27/01	N/A N/A	FDA Fax with Comments Telephone conversations between FDA and BI	11/15/01 12/12-13/01
134	• Protocol Amendment - • Changes in Protocol 1182.41 Amendments 2 and 3 • New Investigators in Protocol 1182.17	12/27/01	 121 125 078 101	 Original Protocol Amendment 1 Original Protocol Amendment 1	 10/30/01 11/13/01 2/12/01 6/25/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
135	• IND Safety Report • Follow-up Report #2 2001-FF-C0384	12/28/01	102 112	Initial Report Follow-up Report #1	7/3/01 8/27/01
136	• Response to FDA Comments in regards to formulation on tipranavir used in preclinical toxicology studies • Information Amendment-Pharmacology/Toxicology/Chemistry, Manufacturing and Control	1/29/02	N/A 100 133	Telephone conversations between BI and FDA Information Amendment – CMC support for on-going and future clinical trails studies. Response to FDA Comments in regards to combination toxicology studies	1/28-1/29/02 6/19/01 12/27/01
137	• Information Amendment: Clinical/Request for Comment-Discontinuation of Tipranavir Study 1182.42	2/14/02	129	Terminated study	12/19/01
138	• Protocol Amendment • New Protocol 1182.12 • Changes in Protoco1 1182.12 Amendment 1	3/4/02	N/A	Clinical Development Meeting between BI and FDA	10/5/01
139	• Response to FDA Request for Information	3/5/02	N/A	FDA Fax	2/15/02
140	• Information Amendment - Pharmacology/Toxicology Reports	3/13/02	N/A	N/A	N/A
141	• General Corresp – BI seeking concurrence with designation of 2 starting materials in the synthesis of TPV	3/21/02	095	General Correspondence – requesting FDA concurrence with designation of starting materials in	6/6/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	tipranavir drug substance			the syntheses of tipranavir drug substance	
142	• Protocol Amendment • New Protocol 1182.55 • Changes in Protocol 1182.55 Amendment 1 • New Investigator for 1182.17	3/26/02	N/A 078 101	N/A Original protocol Amendment 1	N/A 2/12/01 6/25/01
143	• Information Amendment - Chemistry, Manufacturing and Control reports	4/3/02	N/A	N/A	N/A
144	• Information Amendment- Pharmacology/Toxicology Reports	4/11/02	N/A	N/A	N/A
145	• IND Safety Report • Follow-up Report #3 2001-FF-C0384(3) • Follow-up Report #1 2001-FF-C0647(1)	4/24/02 4/24/02	 102 112 135 119	 Initial Report Follow-up Report #1 Follow-up Report #2 Initial Report	 7/3/01 8/27/01 12/28/01 410/15/01
146	• Information Amendment – Clinical Investigators Brochure Version 5	4/26/02	N/A	N/A	N/A
147	• IND Safety Report Follow-up Report #4 2001-FF-0384(4)	4/29/02	102	Initial Report	7/3/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			112 135 145	Follow-up Report #1 Follow-up Report #2 Follow-up Report #3	8/27/01 12/28/01 4/24/02
148	• IND Safety Report • Follow-up Report #3 2001-DE-05034(3) • Follow-up Report#2 2001-FF-C0647(2)	5/7/02	 093 105 131 119 145	 Initial Report Follow-up Report#1 Follow-up Report#2 Initial Report Follow-up Report#1	 5/29/01 8/1/01 12/20/01 10/15/01 4/22/02
149	• Protocol Amendment - Changes in Protocol 1182.12 Amendment 2	5/15/02	138	Original Protocol Amendment 1	3/4/02 3/4/02
150	• Response to FDA Request for Information – providing information on the in-life data at 3 months from the ongoing six-month rat and dog toxicology studies, the oral toxicity of polyoxy135 castor oil in animals and SEDDS formulations used for other drugs in preclinical/clinical trials	5/17/02	N/A 139	Telephone conversation between FDA and BI Response to FDA Request for Information	2/15/02 3/5/02
151	• Information Amendment: Pharmacology/Toxicology report • Request for FDA Feedback – BI seeking FDA concurrence with dose selection for the TPV/RTV and RTV groups for 2-year	5/24/02	048 N/A	Request for Carcinogenicity Study Protocol FDA Fax	5/19/99 5/19/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	rat carcinogenicity study		N/A	Telephone conversation between BI and FDA	4/18/02
152	• Protocol Amendment - New Investigators • 1182.52 • 1182.55	5/24/02	138 149 142	Original Protocol and Amendment 1 Amendment 2 Original Protocol and Amendment 1	3/4/02 5/15/02 3/26/02
153	• IND Safety Report • Follow-up Report #4 2001-DE-05034(4)	5/31/02	093 105 131 148	Initial Report Follow-up Report #1 Follow-up Report #2 Follow-up Report #3	5/29/01 8/1/01 12/20/01 5/7/01
154	• Protocol Amendment - Changes in Protocol 1182.17 Amendment 2	6/12/02	078 101	Original Protocol Amendment 1	2/12/01 6/25/01
155	• Protocol Amendment - New Investigators for 1182.52	6/14/02	138 149	Original Protocol and Amendment 1 Amendment 2	3/4/02 5/15/02
156	• Information Amendment - Chemistry, Manufacturing and Control	6/28/02	N/A	N/A	N/A
157	• Protocol Amendment-Changes in Protocol 1182.55 Amendment 2 and 3	7/2/02	142	Original Protocol and Amendment 1	3/26/02
158	• IND Safety Report • Initial Report 2002-FF-00410FF(0)	7/9/02	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
159	• Information Amendment-Chemistry, Manufacturing and Control	7/15/02	N/A	N/A	N/A
160	• General Correspondence - Discontinuation of Tipranavir Study 1182.22	7/17/02	142 157	1182.55 Original Protocol and Amendment 1 Amendments 2 and 3	3/26/02 7/2/02
			138 149 149	1182.52 Original Protocol and Amendment 1 Amendment 2	3/4/02 5/15/02
			078 101 152	1182.55 Original Protocol Amendment 1 Amendment 2	2/12/01 6/25/01 6/12/02
161	• Request for Special Protocol Assessment-Clinical BI requests special protocol assessment of 1182.12	7/18/02	N/A	BI and FDA meet for Type C Meeting	10/5/01
			115	Desk Copies of General Correspondence - Background Document for Type C Meeting	9/18/01
			138	Original Protocol Amendment 1	3/4/02
			149	Amendment 2	5/15/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
162	• Information Amendment-Pharmacology/Toxicology Reports • Request for FDA Feedback/Teleconference – BI request concurrence with lowering dose level of ritonavir	7/19/02	151 N/A N/A	Information Amendment – Pharmacology/Toxicology FDA Fax accepting proposed dose levels BI email to FDA requesting rapid agreement on ritonavir dose in study	5/24/02 6/25/02 6/15/02
163	• IND Safety Report • Follow-up Report #1 2002-FF-0041OFF (1)	7/23/02	158	Initial Report	7/9/02
164	• IND Safety Report • Follow-up Report #2 2002-FF-00410FF (2)	8/1/02	158 163	Initial Report Follow-up #1	7/9/02 7/23/02
165	• IND Safety Reports • Follow-up Report #3 2002-FF-00410ff(3) • Initial Report 2002-BP-03629BP(0)	8/12/02	158 163 164 N/A	Initial Report Follow-up #1 Follow-up #2 7-Day fax	7/9/02 7/23/02 8/1/02 8/5/02
166	• Protocol Amendment – • New Investigator for 1182.55 • Changes in Protocol 1182.55 Amendment 4	8/15/02	142 157	Original Protocol and Amendment 1 Amendment 2 and 3	3/26/02 7/2/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
167	• IND Safety Reports • Initial and Follow-up #1 2002-FF-00494FF(0)/(1)	8/23/02	N/A	N/A	N/A
168	• IND Safety Report • Follow-up report #2 2002-FF-00494FF(2)	8/27/02	167 167	Initial Report Follow-up #1	8/23/02 8/23/02
169	• IND Safety Report • Follow-up Report #4 2002-FF-00410FF(4)	8/28/02	158 163 164 165	Initial Report Follow-up #1 Follow-up #2 Follow-up #3	7/9/02 7/23/02 8/1/02 8/12/02
170	• IND Safety Report • Follow-up Report #5 2002-FF-00410FF(5) • Follow-up Report #1 2002-BP-03629BP(1)	9/6/02	158 163 164 165 169 165	Initial Report Follow-up#1 Follow-up#2 Follow-up#3 Follow-up#4 Initial Report	7/9/02 7/23/02 8/1/02 8/12/02 8/28/02 8/12/02
171	• IND Safety Report • Follow-up #3 2001-FF-C0647(3)	9/12/02	119 145 148	Initial Report Follow-up #1 Follow-up #2	10/15/01 4/24/02 5/7/02
172	• IND Safety Report • Follow-up #3 2002-FF-00494FF(3)	9/18/02	167 167 168	Initial Report Follow-up #1 Follow-up #2	8/23/02 8/23/02 8/27/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
173	• IND Safety Report • Follow-up Report #2 2002-BP-03629BP(2) • Follow-up Report #3 2002-BP-03629BP(3)	9/20/02	165 170	Initial Report Follow-up#1	8/12/02 9/6/02
174	• General Correspondence – Administrative Information for September 27, 2002 teleconference between BI and FDA to discuss BI's proposal for designation of 4 TPV as a starting material in the synthesis of tipranavir drug substance	9/20/02	141 N/A N/A	General Correspondence – BI seeking concurrence with designation of two starting materials in the synthesis of tipranavir drug substance BI fax to FDA FDA Letter re: comments on 1182.12 and drug interaction program	3/21/02 8/2/02 8/29/02 9/20/02
175	• Information Amendment-Pharmacology/Toxicology Reports	10/8/02	N/A	N/A	N/A
176	• Request for Type B Meeting - End of Phase II • Request for Teleconference-Clinical/Pharmacokinetics	10/11/02	N/A 123 138	BI and FDA Meeting –Type C Meeting minutes issued Protocol 1182.52 submitted	10/5/01 11/7/01 3/4/02
177	• Request for Type B Meeting - End of Phase II (CMC)	10/11/02	N/A	Meeting Request	

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
178	• IND Safety Reports • Initial Report 2002-FF-00587FF(0) • Follow-up #4 2002-FF-00494FF(4)	10/16/02	 N/A 167 167 168 172	 N/A Initial Report Follow-up #1 Follow-up #2 Follow-up #3	 N/A 8/23/02 8/23/02 8/27/02 9/18/02
179	• IND Safety Report • Initial Report 2002-IT-00096IT(0)	10/24/02	N/A	N/A	N/A
180	• IND Safety Report • Follow-up #4 2002-BP-03629BP(4) • Follow-up #6 2002-FF-00410FF(6)	10/29/02	 165 170 173 173 158 163 164 165 169 170	 Initial Report Follow-up # 1 Follow-up # 2 Follow-up # 3 Initial Report Follow-up # 1 Follow-up # 2 Follow-up # 3 Follow-up # 4 Follow-up # 5	 8/12/02 9/6/02 9/20/02 9/20/02 7/9/02 7/23/02 8/1/02 8/12/02 8/28/02 9/6/02
181	• Response to FDA Comments - FDA Letters re: Special Protocol Assessment, Protocol 1182.12 and ddI Drug Interaction	10/30/02	N/A 161	FDA Letter Protocol for Request for Special Protocol Assessment	8/29/02 7/19/02

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			N/A	FDA Fax	9/20/02
			N/A	Telecon between BI and FDA	9/20/02
			137	Information Amendment: Clinical/Request for Comment- Discontinuation of Tipranavir Study 1182.42	10/11/02
			176	Request for Type B Meeting – End of Phase II and Request for teleconference	
182	• General Correspondence – Feedback from IRB's refusing to conduct study • Request for Feedback • Drug Interaction Study with abacavir	11/8/02	N/A	FDA and BI Meeting	10/5/01
183	• Information Amendment - Chemistry, Manufacturing and Control	11/13/02	N/A	N/A	N/A
184	• Type B Background Document for End of Phase II Meeting scheduled for December 18, 2002	11/14/02	177	Type B End of Phase II meeting request	10/11/02
185	• Information Amendment- Pharmacology/Toxicology Reports	11/14/02	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
186	• General Correspondence - Background Document for End of Phase II Meeting	11/15/02	176	Request for Type B End of phase 2 Meeting	10/11/02
			N/A	Telephone conversation between BI and FDA	10/31/02
			161	Request for a Special protocol Assessment	7/18/02
			N/A	FDA Fax	8/28/02
			N/A	FDA Fax	9/20/02
			181	Response to FDA Comments - FDA Letters	10/30/02
			N/A	FDA Fax "Overview of Pharmacology/Toxicology comments regarding the clinical development of tipranavir"	10/30/02
187	• Response to FDA Comments – Overview of Pharmacology/Toxicology comments	11/18/02	N/A	FDA Fax	10/30/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	regarding the clinical development program for tipranavir		181	Response to FDA Comments - FDA Letters	10/30/02
188	• IND Safety Report • Follow-up #5 2002-FF-00494FF(5)	11/20/02	167 167 168 172 178	Initial Report Follow-up # 1 Follow-up # 2 Follow-up # 3 Follow-up # 4	8/23/02 8/23/02 8/27/02 9/18/02 10/16/02
189	• IND Safety Report • Follow-up #1 2002-FF-00587FF(1)	11/20/02	178	Initial Report	10/16/02
190	• Protocol Amendment- • New Investigators for 1182.17	11/26/02	 078 101 154	 Original Protocol Amendment 1 Amendment 2	 2/12/01 6/25/01 6/12/02
191	• General Correspondence - Chemistry, Manufacturing and Controls, BI providing current specifications for 2 TPV and information regarding m-nitropropriophenone (*m*-NPP)	12/11/02	N/A N/A N/A	BI and FDA Teleconference FDA Meeting Minutes BI and FDA telephone conversation	9/27/02 10/7/02 7/18/01
192	• Type B Background Document - Chemistry, Manufacturing and Control Revised Pages	12/11/02	184	Type B Background Document - Chemistry, Manufacturing and Control	11/14/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
193	• IND Safety Report • Follow-up Report #1 2002-IT-00096IT(1)	12/11/02	179	Initial Report	10/24/02
194	• General Correspondence - Background Document for End of Phase 2 meeting	12/13/02	186	General Correspondence - Background Document for End of Phase 2 Meeting	11/15/02
195	• Response to FDA Comments – Clinical and Clinical Pharmacology comments regarding tipranavir	12/13/02	N/A	BI and FDA telephone conversation	12/13/02
196	• General Correspondence - Request for FDA Feedback regarding proposal for the study of oral Cremophor EL human exposure	12/13/02	N/A	BI and FDA teleconference	12/4/02
197	• IND Safety Report • Follow-up #5 2002-BP-0362BP(5)	12/26/02	165 170 172 173 180	Initial Report Follow-up # 1 Follow-up # 2 Follow-up # 3 Follow-up # 4	8/15/02 9/12/02 9/18/02 9/20/02 10/29/02
198	• IND Safety Report- • Initial Report 2002-BP-0617BP(0)	12/30/02	N/A	N/A	N/A
199	• Information Amendment-Pharmacology/Toxicology, New Protocol	12/31/02	N/A	BI and FDA teleconference	12/13/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
200	• IND Annual Report – reporting period October 29, 2001- October 30, 2002	1/3/03	N/A	N/A	N/A
201	• IND Safety Report • Follow-up #1 2002-BP-06174BP(1)	1/10/03	198	Initial Report	12/30/02
202	• IND Safety Report • Follow-up #2 2002-BP-06174BP(1)	1/22/03	198 201	Initial Report Follow-up #1	12/30/02 1/10/03
203	• General Correspondence – • Request for Feedback regarding BI's approach for the early access program • Draft Emergency Use (Compassionate Use) Protocol 1182.XX • Draft Expanded Access Protocol Concept Sheet	1/24/03	N/A	End of Phase II Meeting	12/17-18/02
204	• Protocol Amendment – New Protocol 1182.51	1/30/03	N/A	End of Phase II Meeting	12/17/02
205	• Protocol Amendment – New Protocol 1182.12	2/4/03	186 N/A	End of Phase II Background Document FDA Letter to BI	11/15/02 12/31/02
206	• General Correspondence- Request for FDA Feedback regarding drug interaction study between tipranavir and atorvastin	2/7/03	N/A	N/A	N/A
207	• Protocol Amendment – Site Specific Protocol 1182.17 Amendments	2/7/03	190	Protocol Amendment – New Investigators for 1182.17	11/26/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
208	• General Correspondence – supply containers having child resistant closures may not be activated	2/13/03	N/A	N/A	N/A
209	• IND Safety Report • Follow-up #6 2002-FF-00494FF(6)	2/20/03	167 167 168 172 178 188	Initial Report Follow-up # 1 Follow-up # 2 Follow-up # 3 Follow-up # 4 Follow-up #5	8/23/02 8/23/02 8/27/02 9/18/02 10/16/02 11/10/02
210	• Information Amendment – Clinical Updated Investigators Brochure Version 6	2/25/03	125	Information Amendment – Clinical Updated Investigators Brochure Version 5	11/13/01
211	• IND Safety Report • Follow-up #3 2002-BP-06147BP(3)	3/3/03	198 201 202	Initial Report Follow-up #1 Follow-up #2	12/30/02 1/10/03 1/22/03
212	• DISCREPENCY WITH SERIAL NO.'S NO SUBMISSION	N/A	N/A	N/A	N/A
213	• General Correspondence – Response to FDA Fax regarding Clinical, Statistical and Microbiology comments for Protocol 1182.12	3/18/03	N/A	FDA Fax FDA Fax	12/31/02 1/3/03
214	• Protocol Amendment – Changes in Protocol 118.12 Amendment 1 and 2	3/19/03	186 205	End of Phase II Background Document Original Protocol	11/15/02 2/4/03

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
215	• Protocol Amendment – New Investigators for Protocol 1182.12	3/21/03	186 205 213	End of Phase II Background Document Original Protocol Amendments 1and 2	11/15/02 2/4/03 3/19/03
216	• Request for Special Protocol Assessment – Carcinogenicity Study Protocol. BI asking FDA concurrence with the mouse carcinogenicity study protocol.	3/24/03	N/A	N/A	N/A
217	• General Correspondence – • BI's End of Phase II Meeting Minutes • Response to FDA Fax – Request to change official meeting minutes	3/24/03	N/A N/A	End of Phase II Meeting FDA Official Meeting Minutes from End of Phase II Meeting	12/18/02 3/14/03
218	• IND Safety Reports • Initial Report 2002-BP-01629BP(0) • Follow-up #6 2002-BP-03629BP(0)	3/27/03	N/A 165 170 172 173 180 197	N/A Initial Report Follow-up # 1 Follow-up # 2 Follow-up # 3 Follow-up # 4 Follow-up #5	N/A 8/15/02 9/12/02 9/18/02 9/20/02 10/29/02 12/26/02
219	• IND Safety Report • Follow-up #1 2003-BP-01629	3/28/03	218	Initial Report	3/27/03

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
220	• Protocol Amendment – Changes in Protocol 1182.12 Amendment 3	3/31/03	186 205 214 N/A	End of Phase II Background Document Original Protocol Amendment 1 and 2 Response to FDA comments	11/15/02 2/4/02 3/19/02 12/31/02
221	• Protocol Amendment – New Protocol 1182.58 Open Label Safety Study	4/3/03	203	General Correspondence – Proposed Emergency Use Program	1/24/03
222	• Protocol Amendment – Changes in Protocol 1182.17 Amendment 3	4/22/03	078 101 154	Original Protocol Amendment 1 Amendment 2	2/12/01 6/25/01 6/12/02
223	• IND Safety Report • Initial Report 2003-CN-00177CN(0)	4/24/03	N/A	N/A	N/A
224	• IND Safety Report • Initial Report 2003-BP-02474AU(0)	4/29/03	N/A	N/A	N/A
225	• IND Safety Report • Follow-up #1 2003-BP-02474AU(1)	5/7/03	224	Initial Report	4/29/03
226	• Protocol Amendment – Changes in Protocol 1182.51 Amendment 1 and 2	5/9/03	204	Original Protocol	1/30/03
227	• Information Amendment – CMC, new documentation for drug substance and drug product to support on-going and future clinical trails	5/13/04	208	General Correspondence – supply containers having child resistant closures may not be activated	2/13/03

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
228	• IND Safety Report • Initial Report 2003-DE-01992DE(0)	6/3/03	N/A	N/A	N/A
229	• IND Safety Report • Follow-up #2 2003-BP-02474AU(2)	6/6/03	224 225	Initial Report Follow-up #1	4/29/03 5/7/03
230	• Protocol Amendment – Change in Protocol 1182.12 Amendment 4	6/10/03	186 205 214 N/A 220	End of Phase II Background Document Original Protocol Amendment 1 and 2 Response to FDA comments Amendment 3	11/15/02 2/4/02 3/19/02 12/31/02 3/31/03
231	• IND Safety Report • Follow-up #1 2003-CN-00177CN(1)	6/13/03	223	Initial Report	4/24/03
232	• Protocol Amendment – New Protocol 1182.24	6/13/03	N/A	N/A	N/A
233	• Protocol Amendment – Change in Protocol 1182.24	6/18/03	232	Original Protocol	6/18/03
235	• IND Safety Report – • Follow-up #3 2003-BP-02474AU(3)	6/19/03	224 225 229	Initial Report Follow-up #1 Follow-up #2	4/29/03 5/7/03 6/6/03

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236	• IND Safety Report – • Follow-up #4 2003-BP-02474AU(4)	6/24/03	 224 225 229 235	 Initial Report Follow-up #1 Follow-up #2 Follow-up #3	 4/29/03 5/7/03 6/6/03 6/19/03
237	• Protocol Amendment – New Investigators for 1182.58	6/27/03	221	Original Protocol	4/3/03
238	• Protocol Amendment – New Investigators • 1182.58 • 1182.51	7/2/03	 186 205 214 220 N/A 204 226	 End of Phase II Background Document Original Protocol Amendments 1 and 2 Amendment 3 Response to FDA Comments Original Protocol Amendment 1	 11/15/02 2/4/03 3/19/03 3/31/03 12/31/02 1/30/03 5/9/03
239	• Protocol Amendment – Changes in Protocol 1182.51 Amendment 3	7/9/03	204 226	Original Protocol Amendment 1 and 2	1/30/03 5/9/03
240	• Response to FDA Request for Information – Comments on Protocol 1182.51	7/14/03	204 226 239 N/A	Original Protocol Amendment 1 and 2 Amendment 3 Fax form FDA	1/30/03 5/9/03 7/9/03 4/14/03
241	• IND Safety Report – Initial Report 2003-BP-04595BP(0)	7/22/03	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
242	• Proposed Changes in Written Request for Pediatric Studies • Proposed Written Agreement for Pediatric Studies • Request for Teleconference to discuss submission	7/23/03	186 N/A N/A N/A	General Correspondence – End of Phase II Background Document, Pediatric Proposal FDA Pediatric Written Agreement End of Phase II Meeting Telephone Conversations between BI and FDA	11/15/02 1/22/03 1/28/03 12/17/02 7/21/03 7/23/03
243	• Information Amendment – Clinical Protocol 1182.17 , first interim safety analyses	7/28/03	078 101 154 222	Original Protocol Amendment 1 Amendment 2 Amendment 3	2/12/01 6/25/01 6/12/02 4/22/03
244	• Protocol Amendment – Pediatric Protocol Submitted for Pediatric Exclusivity Study	8/8/03	242	• Proposed Changes in Written Request for Pediatric Studies • Proposed Written Agreement for Pediatric Studies • Request for Teleconference to discuss submission	7/23/03
245	• IND Safety Report – • Follow-up #1 2003-BP-04595BP(1)	8/19/03	241	Initial Report	7/22/03

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
246	• IND Safety Report – • Initial Report 2003-BP-06107BP(0)	8/29/03	N/A	N/A	N/A
247	• Protocol Amendment – Changes in Protocol 1182.17 Amendment 4	9/4/03	078 101 154 222	Original Protocol Amendment 1 Amendment 2 Amendment 3	2/12/01 6/25/01 6/12/02 4/22/03
248	• IND Safety Report • Follow-up Report #2 2003-BP-04595BP(2)	9/9/03	 241 245	 Initial Report Follow-up #1	 7/22/03 8/19/03
249	• Protocol Amendment – New Investigators for 1182.58	9/9/03	186 205 214 220 N/A	End of Phase II Background Document Original Protocol Amendments 1 and 2 Amendment 3 Response to FDA Comments	11/15/02 2/4/03 3/19/03 3/31/03 12/31/02
250	• Protocol Amendment – New Investigators • 1182.12 • 1182.17	9/12/03	 186 205 214 220 N/A 078 101 154 222	 End of Phase II Background Document Original Protocol Amendment 1 and 2 Amendment 3 Response to FDA comments Original Protocol Amendment 1 Amendment 2	 11/15/02 2/4/02 3/19/02 3/31/03 12/31/02 2/12/01 6/25/01 6/12/02 4/22/03

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			247	Amendment 3 Amendment 4	9/4/03
			232	Original Protocol	6/13/03
	• 1182.24		204		1/30/03
	• 1182.51		226	Original Protocol Amendment 1 and 2	5/9/03
251	• IND Safety Report – • Initial Report 2003-BP-06679BP9)	9/22/03	N/A	N/A	N/A
252	• Information Amendment – Clinical BI Trial No. 1182.41	9/23/03	N/A	N/A	N/A
253	• Protocol Amendment – New Investigator for 1182.24 • Correction of error in Serial Number Assignments	9/24/03	250	Telephone between BI and FDA conversation regarding SN 250	9/24/03
			250	Protocol Amendment – New Investigators	9/12/03
			251	IND Safety Report Initial Report 2003-BP-06679BP9)	9/22/03
			252	Information Amend – Clinical	9/23/03
254	• Request for Special Protocol Assessment – Clinical, Naïve Trial 1182.33	9/26/03	N/A	End of Phase II Meeting between BI and FDA	12/17/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
255	• Information Amendment – Pharmacology/Toxicology - 26-week Safety Study of TPV/RTV SEDDS in Beagle Dogs – 13 week draft interim report	9/26/03	N/A 199 196	BI and FDA Teleconference Information Amendment-Pharmacology/Toxicology, New Protocol General Correspondence - Request for FDA Feedback regarding proposal for the study of oral Cremophor EL human exposure	12/13/02 12/31/02 12/13/03
256	• Information Amendment –New Protocol 1182.45	10/3/03	N/A	N/A	N/A
257	• IND Safety Report • Initial Report 2003-BP-06917BP(0) • Follow-up #1 2003-BP-06679BP(1)	10/6/03	 N/A 250	 N/A Initial Report	 N/A 9/22/03
258	• IND Safety Report • Initial Report 2003-BP-07417BP(0)	10/16/03	N/A	N/A	N/A
259	• IND Safety Report • Follow-up #1 2003-DE-01992DE(1)	10/21/03	228	Initial Report	6/3/03
260	• Information Amendment - Chemistry, Manufacturing and Controls • Drug product documentation for new dosage form, oral solution	11/10/03	244	Protocol Amendment – Pediatric Protocol Submitted for Pediatric Exclusivity Study	8/11/03

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
261	• IND Safety Reports • Initial Report 2003-DE-04674DE(0) • Initial Report 2003-DE-05569DE(0) • Initial Report 2003-BP-09236BP(0)	11/10/03	N/A	N/A	N/A
262	• Protocol Amendment – New Investigators for 1182.58	11/13/03	221	Original Protocol	4/3/03
263	• Information Amendment – Clinical BI Trial 1182.52 Clinical Trial Report	11/14/03	N/A 115 138 149	BI and FDA meet for Type C Meeting Desk Copies of General Correspondence - Background Document for Type C Meeting Original Protocol Amendment 1&Amendment 2	10/5/01 9/18/01 3/4/02 5/15/02
264	• IND Safety Report • Follow-up #1 2003-DE-05569DE(1)	1/17/03	261	Initial Report	11/10/03
265	• Information Amendment – Clinical, Response to FDA Request for information on *in vitro* Selection of Virus Resistant to Tipranavir	11/20/03	Telecon 186	FDA tele call requesting a summary of studies on the *in vitro* selection of virus selection of virus resist to TPV General Correspondence - Background Doc for End of Phase	10/24/03 11/15/02

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				II Meeting	
266	• IND Safety Report • Follow-up #1 2003-DE-09236BP(1)	11/21/03	261	Initial Report	11/10/03
267	• IND Safety Report • Initial Report 2003-BP-09788BR(0)	12/1/03	N/A	N/A	N/A
268	• IND Safety Report • Initial Report 2003-DE-06008GB(0)	12/3/03	N/A	N/A	N/A
269	• IND Safety Report • Initial Report 2003-BP-09687BP(0)	12/4/03	N/A	N/A	N/A
270	• IND Safety Report • Follow-up #1 2003-DE-06008GB(1)	12/15/03	268	Initial Report	12/3/03
271	• IND Safety Report • Follow-up #1 2003-BP-09788BR(1)	12/19/03	267	Initial Report	12/1/03
272	• IND Safety Report • Initial Report 2003-BP-10718BP(0)	12/23/03	N/A	N/A	N/A
273	• IND Safety Reports • Follow-up #2 2003-DE-06008GB(2) • Follow-up #1 2003-BP-10718BP(1)	12/30/03	268 270 272	Initial Report Follow-up #1 Initial Report	12/3/03 12/15/03 12/23/03
274	• IND Safety Report • Initial Report 2003-FF-00627FF(0)	12/30/03	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
275	• IND Safety Report • Follow-up #2 2003-BP-09788BR(2)	12/31/03	 267 271	 Initial Report Follow-up #1	 12/1/03 12/19/03
276	• Information Amendment – Clinical • Request for FDA Comments on Special Protocol Assessment for Protocol 1182.12 (RESIST 1)		161 161 186	Special Protocol Assessment for Protocol 1182.12 (RESIST 1) FDA Comments re: Special Protocol Assessment for Protocol 1182.12 (RESIST 1) BI Response to FDA Comments on Special Protocol Assessment (RESIST 1)	7/18/02 9/20/02 11/15/02
277	• General Correspondence – Safety Information for January 8th telecon		205 214 220 230 078 101 154 222 247	Original Protocol (1182.12) Amendment 1 and 2 (1182.12) Amendment 3 (1182.12) Amendment 4 (1182.12) Original Protocol (1182.17) Amendment 1 (1182.17) Amendment 2 (1182.17) Amendment 3 (1182.17) Amendment 4 (1182.17)	2/4/03 3/19/03 3/31/03 6/10/03 2/12/01 6/25/01 6/12/02 4/22/03 9/4/03

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
278	• General Correspondence – Response to Statistical Comments to Protocol 1182.12 (RESIST 2) Amendment 2	1/7/04	N/A 205 214 220 230	FDA Statistical Comments Original Protocol Amendment 1 and 2 Amendment 3 Amendment 4	9/16/03 2/4/03 3/19/03 3/31/03 6/10/03
279	• Response to Request for Information – AEs and SAEs	1/9/04	N/A N/A 277	Email sent to BI form FDA Teleconference between BI and FDA General Correspondence – Safety Information for January 8th telecon	1/8/04 1/8/04 1/7/04
280	• General Correspondence – Safety Information for January 16, 2004 Meeting to discuss adverse event info	1/12/04	279	Response to Request for Information – AEs and SAEs	1/9/04
281	• IND Safety Report • Initial Report 2003-BP-10942BP(0)	1/12/04	N/A	N/A	N/A
282	• IND Safety Report • Initial 2003-FF-00644FF(0)	1/12/04	N/A	N/A	N/A
283	• General Correspondence – Correction of Attachment 1 and 2 of SN 280 and Safety Information for January 16, 2004 Meeting	1/13/04	280	General Correspondence – Safety Information for January 16, 2004 Meeting to discuss adverse event information for tipranavir	1/12/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
284	• Response to FDA Request for Information – Clinical Safety Information	1/14/04	N/A	Telephone conversation between BI and FDA	1/12/04
285	• Response to FDA Request for Information – Safety Policies and TPV Rick Benefit	1/14/04	N/A	Telephone conversation between BI and FDA	1/12/04
			277	General Correspondence – Safety Information for January 8th telecon	1/7/04
			284	Response to FDA Request for Information – Clinical Safety Information	1/14/04
286	• Protocol Amendment – New Investigators for 1182.17	1/19/04	078	Original Protocol	2/12/01
			101	Amendment 1	6/25/01
			154	Amendment 2	6/12/02
			222	Amendment 3	4/22/03
			247	Amendment 4	9/4/03
			250	Amendment 5	9/4/03
287	• Information Amendment – Clinical - data from human Cremophor EL assay	1/19/04	N/A	Teleconference between BI and FDA	12/4/02
			196	General Correspondence - Request for FDA Feedback regarding proposal for the study of oral Cremophor EL human exposure	12/13/02
				Information Amendment –	9/26/03

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			255	Pharmacology/Toxicology - 26-week Safety Study of TPV/RTV SEDDS in Beagle Dogs – 13 week draft interim report	
288	• IND Safety Report • Initial Report 2004-BP-00114BP(0)	1/20/04	N/A	7-day facsimile	1/15/04
289	• Clinical Information Amendment – Fatal Cases for Submission • Initial Report 2003-DE-06498DE(0) • Initial Report 2004-BP-00054BP(0) • Initial Report 2004-UK-00030UK(0)	1/20/04	N/A 280	Meeting between BI and FDA General Correspondence – Safety Information for January 16, 2004 Meeting to discuss adverse event information for tipranavir	1/16/04 1/12/04
290	• IND Safety Report • Follow-up #3 2003-DE-06008GB(3)	1/23/04	268 270 273	Initial Follow-up #1 Follow-up #2	12/3/03 12/15/03 12/30/03
291	• Protocol Amendment – New Investigators for 1182.58	1/23/04	N/A 115 138 149	BI and FDA meet for Type C Meeting Desk Copies of General Correspondence - Background Document for Type C Meeting Original Protocol Amendment 1&2	10/5/01 9/18/01 3/4/02 5/15/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
292	• IND Safety Report • Follow-up #1 2003-FF-00644FF(1)	1/26/04	 282	 Initial Report	 1/12/04
293	• IND Safety Report • Initial Report 2004-FF-00026FF(0)	1/26/04	N/A	N/A	N/A
294	• IND Safety Report • Initial Report 2003-BP-07128BP(0)	1/27/04	N/A	N/A	N/A
295	• IND Safety Report • Initial Report 2004-BP-00396BP(0)	1/27/04	N/A	N/A	N/A
296	• IND Safety Report • Initial Report 2004-UK-00057UK(0) • Follow-up #1 2003-BP-07128BP(1)	1/30/04	 N/A 294	 N/A Initial Report	 N/A 294
297	• Request for Type B Meeting – Pre-NDA Meeting	1/30/04	N/A	N/A	N/A
298	• Information Amendment – Clinical Safety Information • 2004-UK-00030UK(2) • 2004-UK-00030UK(2)	2/2/04	N/A	N/A	N/A
299	• General Correspondence – drafted revision to corporate Standard Operating Procedures (SOPs) regarding adverse event reporting	2/2/04	N/A	BI/FDA Meeting	1/16/04
300	• IND Safety Report • Initial 2003-BP-08944BP(0)	2/2/04	N/A	7 Day Facsimile	1/27/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
301	• IND Safety Report • Initial 2004-DE-00370GB(0)	2/5/04	N/A	N/A	N/A
302	• General Correspondence – BI Meeting minutes from face to face meeting	2/5/04	N/A	BI/FDA Meeting	1/16/04
303	• IND Annual Report – Reporting period 10/1/02 – 9/30/03	2/6/04	N/A	N/A	N/A
304	• IND Safety Report • Follow-up #4 2003-DE-06008GB(4)	2/6/04	268 270 273 290	Initial Follow-up #1 Follow-up #2 Follow-up #3	12/3/03 12/15/03 12/30/03 1/23/04
305	• Information Amendment – Clinical Safety Information • 2003-DE-03576GB(0) • 2003-DE-03806DE(0) 2003-BP-05935BP(0)	2/6/04	N/A 284	BI/FDA Meeting Response to FDA Request for Information	1/16/04 1/14/04
306	• Protocol Amendment – Changes in Protocol 1182.14 Amendment 1	2/6/04	244	Original Protocol	8/8/03
307	• General Correspondence – Request for Evaluation of Trade name	2/6/04	N/A	N/A	N/A
308	• IND Safety Report • Follow-up #1 2003-BP-08944BP(1) • Follow-up #1 2004-BP-00114BP(1)	2/9/04	 300 N/A 288 N/A	 Initial Report 7 day facsimile Initial Report 7 day facsimile	 2/2/04 1/27/04 1/20/04 1/15/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
309	• Information Amendment – Clinical Safety Information • 2003-FF-00246FF(0) • 2003-UK-00670UK(0)	2/9/04	N/A	N/A	N/A
310	• Information Amendment – Clinical Safety Information • 2004-BP-0677BP(0)	2/12/04	N/A	N/A	N/
311	• Information Amendment – Clinical Safety Information • January 2004 Monthly Report	2/12/04	N/A	BI/FDA Meeting	N/A
312	• Information Amendment – Clinical Safety Information;2003-BP-09677BP(0) • 2003-BP-06681BP(0) • 2004-IT-00012IT(0)/ • 2004-BP-00825BR(0)	2/13/04	284	Response to FDA Request for Information	1/14/04
313	• IND Safety Report • Follow-up #1 2004-UK-00057UK(1	2/13/04	296	Initial Report	2/13/04
314	• Request for Type B Meeting – CMC Pre-NDA Meeting	2/17/04	260	Information Amendment – CMC Drug product documentation for new dosage form, oral solution	10/29/03
315	• Information Amendment – Clinical Safety Information • 2004-FF-00088FF(0)	2/18/04	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	• 2003-BP-09677BP(0) • 2004-BP-00825BR(0) • 2004-BP-00677BP(0)		284 312 312 310	Initial Report Follow-up #1 Initial Report Initial Report	1/14/04 2/13/04 2/13/04 2/18/04
316	• IND Safety Report • Follow-up #1 2004-DE-00370GB(1)	2/18/04	301	Initial Report	2/5/04
317	• Information Amendment – Pharm/Tox	2/20/04	N/A	N/A	N/A
318	• General Correspondence – Request for FDA Feedback in regards to BI's plans for immunotoxicology testing for Tipranavir	2/20/04	N/A	N/A	N/A
319	• Information Amend – Clin Safety Info	2/23/04	N/A	N/A	N/A
320	• IND Safety Report • Follow-up #2 2003-BP-08944BP(2)	2/24/04	300 308	Initial Report Follow-up #1	2/2/04 2/9/04
321	• IND Safety Report • Follow-up #5 2003-DE-06008GB(5)	2/25/04	268 270 273 290 304	Initial Follow-up #1 Follow-up #2 Follow-up #3 Follow-up #4	12/3/03 12/15/03 12/30/03 1/23/04 2/6/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
322	• Information Amendment – Clinical Safety Information • 2004-IT-00024IT(0)	2/26/04	N/A	N/A	N/A
323	• IND Safety Report • Follow-up #1 2003-BP-10942BP(1)	2/27/04	281	Initial Report	1/12/04
324	• Information Amendment – Pharm/Tox U04-3011	2/27/04	N/A	N/A	N/A
325	• Information Amendment – Clinical Safety Information	3/1/04	N/A	N/A	N/A
326	• IND Safety Report Follow-up #2 2004-DE-00370GB(2) Initial 2004-FF-00117FF(0)	3/1/04	300 316	Initial Report Follow-up #1	2/5/04 2/18/04
327	• IND Safety Report • Initial 2004-SW-00048SW(0)	3/1/04	N/A	7 day facsimile	2/24/04
328	• Protocol Amendment – New Investigators for 1182.58	3/3/04	221	Original Protocol	4/3/04
329	• IND Safety Report • Follow-up #1 2004-UK-00057UK(2) • Follow-up #2 2003-BP-10718BP(2)	3/5/04	 296 313 272 274	 Initial Report Follow-up #1 Initial Report Follow-up #1	 1/30/04 2/13/04 12/23/03 12/30/03
330	• Information Amendment – Clinical	3/5/04			

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	Safety Information • 2004-BP-00677BP9(0) • 2003-BP-10111BP(0)		N/A 310 315 325 284	7-day facsimile Initial Report Follow-up #1 Follow-up #2 Initial Report	2/2/04 2/12/04 2/18/04 3/1/04 1/14/04
331	• Information Amendment – Clinical Safety Information	3/8/04	N/A	N/A	N/A
332	• IND Safety Report • Initial 2003-BP-068455P(0) • Follow-up #1 2003-BP-09687BP(1)	3/9/04	NA 269	N/A Initial Report	N/A 12/4/03
333	• IND Safety Report • Initial 2003-BP-01512AU(0) • Follow-up #1 2003-DE-04674DE(1)	3/9/04	N/A 261	N/A Initial Report	N/A 11/10/03
334	• Information Amendment – Clinical Safety Information	3/10/04	N/A	N/A	N/A
335	• IND Safety Report • Follow-up #3 2003-BP-10718BP(3)	3/10/04	272 274 329	Initial Report Follow-up #1 Follow-up #2	12/23/03 12/30/03 3/5/04
336	• Information Amendment – Clinical Safety Information • 2003-BP-10241BP(1) • 2003-FF-00105FF(0)	3/12/04	284 N/A 325	Initial Report 7-day facsimile Initial Report	1/14/04 2/23/04 3/1/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
337	• Information Amendment – Clinical Safety Information February 2004 Monthly Report	3/12/04	N/A	BI/FDA Meeting	1/16/04
338	• IND Safety Report • Follow-up #3 2004-DE-00370GB(3)	3/12/04	300 316 326	Initial Report Follow-up #1 Follow-up #2	2/5/04 2/18/04 3/1/04
339	• Protocol Amendment – New Investigators for 1182.17	3/12/04	078 101 154 222 247	Original Protocol Amendment 1 Amendment 2 Amendment 3 Amendment 4	2/12/01 6/25/01 6/12/02 4/22/03 9/4/03
340	• Response to FDA Request – Review of Mortality Rates • Request for Teleconference to discuss this information, answer any questions and receive feedback •	3/12/04	N/A	BI/FDA Teleconference	2/19/04
341	• IND Safety Report • Follow-up #3 2004-UK-00057UK(3)	3/15/04	296 313 329	Initial Report Follow-up #1 Follow-up #2	1/30/04 2/13/04 3/5/04
342	• Information Amendment – Clinical Safety Information	3/15/04	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
343	• Information Amendment – CMC providing new and updated CMC documentation for drug substance	3/15/04	N/A	N/A	N/A
344	• Information Amendment – Clinical Safety Information • 2004-FF-00058FF(0)	3/16/04	N/A	N/A	N/A
345	• Information Amendment – Clinical Safety Information • 2004-BP-01447BP(0) • 2003-BP-10562BP(0)	3/17/04	N/A 331 N/A 342	7-day facsimile Initial Report 7-day facsimile Initial Report	3/1/04 3/8/04 3/15/04 3/15/04
346	• General Correspondence – Pre-NDA Meeting Package • Request for Teleconference to discuss key clinical, statistical and format topics prior to face-to-face meeting	3/17/04	297 N/A	Request for Pre-NDA Meeting BI/FDA Telephone conversation	1/30/04 2/12/04
347	• IND Safety Report • Initial 2004-FF-00125FF(0)	3/18/04	N/A	N/A	N/A
348	• IND Safety Report • Follow-up #1 2003-BP-06845BP(1)	3/19/04	332	Initial Report	3/9/04
349	• Information Package for Type B Pre-NDA Meeting – CMC	3/19/04	314 N/A	Request for Type B Meeting Pre-NDA Meeting CMC End of Phase II Meeting	2/17/04 12/18/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
350	• Protocol Amendment – Changes in Protocol 1182.58 Amendment 2	3/19/04	221 N/A	Original Protocol BI/FDA Meeting	4/3/03 1/16/
351	• Information Amendment – Clinical Safety Information	3/19/04	N/A	N/A	N/A
352	• IND Safety Report • Initial 2004-FF-00125FF(0)	3/19/04	347	Originally submitted without case narrative and the like analysis report	3/18/04
353	• Information Amendment – Clinical Safety Information	3/22/04	N/A	N/A	N/A
354	• IND Safety Report • Follow-up #6 2003-DE-06008GB(6)	3/22/04	268 270 273 290 304 321	Initial Follow-up #1 Follow-up #2 Follow-up #3 Follow-up #4 Follow-up #5	12/3/03 12/15/03 12/30/03 1/23/04 2/6/04 2/25/04
355	• Information Amendment – Pharm/Tox U04-3013, U04-3034-02, U04-3035, U04-3036, U04-3037	3/23/04	N/A	N/A	N/A
356	• Information Amendment – Clinical Safety Information • 2004-BP-01804BP(0) 2004-BP-00953BR(0)	3/23/04	 N/A N/A	 N/A 7 day fax	 N/A 3/16/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
357	• Information Amendment – Clinical U04-3025, U04-3026 and U04-3027	3/23/04	N/A	N/A	N/A
358	• Information Amendment – Clinical Safety Information	3/24/04	N/A	N/A	N/A
359	• IND Safety Report • Follow-up #2 2004-BP-00114BP(2) • Follow-up #3 2003-BP-04595BP(3)	3/24/04	 288 308 241 245 248	 Initial Report Follow-up #1 Initial Report Follow-up #1 Follow-up #2	 1/20/04 2/9/04 7/22/03 8/19/03 9/9/03
360	• IND Safety Report • Follow-up #2 2003-BP-10942BP(2)	3/26/04	 281 323	 Initial Report Follow-up #1	 1/12/04 2/27/04
361	• Information Amendment – Clinical Safety Information • 2003-BP-06941AU(1) • 2004-FF-00058FF(0)	3/29/04	 N/A 342 N/A 344 353	 7-day fax Initial Report 7-day fax Initial Report Follow-up #1 – ck on this	 3/3/04 3/15/04 3/10/04 3/16/04 3/22/04
362	• IND Safety Report • Follow-up #1 2004-FF-00125FF(1)	3/30/04	347 352	Initial Report Replacement of Initial Report	3/18/04 3/19/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
363	• IND Safety Report • Follow-up #1 2003-BP-06917BP(1)	3/31/04	257	Initial Report	10/6/03
364	• IND Safety Report • Follow-up #1 2003-P-01512AU(1)	3/31/04	333	Initial Report	3/9/04
365	• Response to FDA Request for Information – Follow-up to Mortality Analysis – CD4 Cell counts/causes of deaths	4/1/04	N/A 340	Telephone conversation Response to FDA Request – Review of Mortality Rates	3/17/04 3/12/04
366	• Information Amendment – Clinical Safety Information	4/1/04	N/A	N/A	N/A
367	• Information Amendment – Clinical Safety Information	4/6/04	N/A	N/A	N/A
368	• IND Safety Report • Follow-up #4 2003-BP-04595(4)	4/6/04	241 245 248 359	Initial Report Follow-up #1 Follow-up #2 Follow-up #3	7/22/03 8/19/03 9/9/03 3/24/04
369	• General Correspondence - Background/Current Safety Reporting Processes and Procedures and Proposed updates to Safety Reporting Processes and Procedures	4/6/04	N/A 302 N/A 285	BI/FDA Meeting BI Meeting Minutes FDA Meeting Minutes Overview of BI's Safety SOP	1/16/04 2/5/04 3/3/04 1/14/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	• Request for Teleconference to assure that BI can implement the new Processes and procedures				
370	• Information Amendment – Clinical Safety Information • 2003-FF-00518FF(3) • 2003-CN-00461CN(1)	4/7/04	 284 319 370 284	 Initial Report Follow-up #1 Follow-up #2 Initial Report	 1/14/04 2/3/04 4/7/04 1/14/04
371	• Information Amendment – Clinical Safety Information • 2003-FF-00518FF(3) • 2003-CN-00461CN(1)	4/7/04	 284 319 370 284	 Initial Report Follow-up #1 Follow-up #2 Initial Report	 1/14/04 2/3/04 4/7/04 1/14/04
372	• IND Safety Report • 2003-BP-08944BP(3)	4/9/04	300 308 320	Initial Report Follow-up #1 Follow-up #2	2/2/04 2/9/04 2/24/04
373	• Information Amendment – Clinical Safety Information	4/9/04	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
374	• Information Amendment – Clinical Safety Information • 2004-BP-02534BP(0) • 2003-FF-00625FF(2)	4/12/04	 N/A N/A 342 367	 7-day facsimile 7-day facsimile Initial Report Follow-up #1	 4/5/04 3/9/04 3/15/04 4/6/04
375	• IND Safety Report • Initial Report 2003-BP-03027BP(0)	4/12/04	N/A	N/A	N/A
376	• IND Safety Report • Follow-up #1 2003-BP-06107BP(1)	4/12/04	 246	 Initial Report	 8/29/03
377	• IND Safety Report • Initial Report 2004-BL-00067BL(0)	4/12/04	N/A	N/A	N/A
378	• Information Amendment – Clinical Safety Information March 2004 Monthly Report	4/13/04	N/A	BI/FDA Meeting	1/16/04
379	• Information Amendment – Clinical Safety Information	4/13/04	N/A	N/A	N/A
380	• IND Safety Reports • Follow-up #2 2003-CN-00177CN(2)	4/13/04	 223 231	 Initial Report Follow-up #1	 4/24/03 6/13/03
381	• Amendment to Information Package for Type B Pre-NDA Meeting	4/13/04	349	Information Package for Type B Pre-NDA Meeting – CMC	3/19/04

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382	• IND Safety Report • Follow-up #3 2004-BP-00114BP(3)	4/14/04	 N/A 288 208 359	 7-day facsimile Initial Report Follow-up #1 Follow-up #2	 1/15/04 1/20/04 2/9/04 3/24/04
383	• Information Amendment:Clinical • Interim Study results of pharmacokinetic study 1182.51	4/15/04	383		
384	Response to Request for Information/Request for Teleconference – Requesting additional information pertaining to the preliminary results from the dual-boosted protease inhibitor pharmacokinetic study, 1182.51	4/15/04	N/A 384	Telefax from FDA Response to FDA Fax of 4/8/04:Preliminary Results from pharmacokinetic study 1182.51	4/8/04 4/15/04
385	• IND Safety Report Follow-up #2 2003-BP-01512AU(2)	4/16/04	333 364	Initial Report Follow-up #1	3/9/04 3/31/04
386	• Information Amendment:Clinical • Investigators Brochure - Version 7	4/16/04	210 125	Information Amendment - Clinical Updated Investigators Brochure Version 6 Information Amendment – Clinical Updated Investigators Brochure Version 5	2/25/03 11/13/01
387	• IND Safety Report Initial Report 2004-FF-00234FF(0)	4/16/04	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
388	• Information Amendment: Clinical Fatal Cases 2003-FF-00640FF(2)	4/20/04	N/A		
389	• IND Safety Report Initial Report 2004-BP-02706BP(0)	4/19/04	N/A	N/A	N/A
390	• Amendment: Clinical Fatal Cases 2003-FF-00640FF(2)	4/20/04	N/A	N/A	N/A
391	• IND Safety Report Follow-up #1 2004-SW-00048SW(1)	4/20/04	327	Initial Report	3/1/04
392	• Response to Request for Information:Tabular Listing of Deaths	4/22/04	384	Telefax from FDA Response to FDA Fax of 4/8/04:Preliminary Results from pharmacokinetic study 1182.51	4/8/04 April 15, 2004
393	• IND Safety Report Initial Report 2004-FF-00256FF(0)	4/26/04	N/A	N/A	N/A
394	• Information Amendment: Clinical Fatal Cases 2003-FF-00367FF(1), 2003-FF-00440FF(2), 2003-CN-00318CN(1) and 2003-BP-10111BP(3)	4/26/04	4/26/04	N/A	N/A
395	• IND Safety Report Initial Report 2004-BP-02978BR9(0)	4/27/04	N/A	N/A	N/A
396	Information Amendment:Clinical Report 1182.22 /U03-3408	4/27/04	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
397	IND Safety Report Follow-up 2004-BP-02706BP(1)	4/28/04	389	Initial Report	4/19/04
398	Information Amendment: Clinical Fatal 2004-FF-00176FF(2), 2003-BP-10111BP(4), 2004-BP-02413AU(1) and 2004-BP-03100MX(0) •	4/29/04	N/A 280	Meeting between BI and FDA General Correspondence – Safety Information for January 16, 2004 Meeting to discuss adverse event information for tipranavir	1/16/04 1/12/04
399	• Information Amendment: Clinical-Safety Information-April 2004 Quarterly Safety Summary	4/30/04	N/A	Meeting w/FDA where BIPI agreed to submit for a period not less than 1 yr: all deaths for unrelated deaths as CIA cases, Grade 3 & 4 serious cases on a monthly basis, and a safety summary on a quarterly basis. (beginning on 1/19/04)	1/16/04
400	General Correspondence: Evaluation of Interactions w/ the agency regarding TPV Development program	4/30/04	 384	Telefax from FDA Response to FDA Fax of 4/8/04:Preliminary Results from pharmacokinetic study 1182.51	April 8, 2004 April 15, 2004
401	• IND Safety Report Follow-up 2003-BP-09788BR(3)	5/03/04	267 271 275	Initial report Follow-up #1 Follow-up #2	12/1/03 12/19/04 12/31/04
402	• Protocol Amendment:New Investigators Study 1182.58	5/03/04	N/A	BI and FDA meet for Type C Meeting	10/5/01

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			115	Desk Copies of General Correspondence - Background Document for Type C Meeting	9/18/01
			138	Original Protocol	3/4/02
			149	Amendment 1& Amendment 2	5/15/02
403	• Information Amendment: Clinical Fatal Cases 2004-ES-00091ES(0)	5/4/04	403	N/A	N/A
404	• Protocol Amendment – Changes in Protocol 1182.17 Amendment 5	5/5/04	078	Original Protocol	2/12/01
			101	Amendment 1	6/25/01
			154	Amendment 2	6/12/02
			222	Amendment 3	4/22/03
			247	Amendment 4	9/4/03
405	• Information Amendment:Clinical 1182.55	5/6/04			
		5/6/04	142	Original Protocol	3/26/02
		7/2/02	142	Amendment 1	3/26/02
			158	Amendment 2	3/26/02
			158	Amendment 3	3/26/02
406	• General Correspondence: CMC Pre-NDA Meeting Minutes	5/7/04	406	Type B pre-NDA Meeting for tipranavir capsules	4/19/04
407	• IND Safety Report Follow-up 2004-FF-00117FF(1)	5/10/04	326	Initial Report	3/1/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
408	• Information Amendment:Clinical Fatal Cases 2004-BP-01767BP(01)	5/10/04		Follow-up Report CIA Case	
409	• IND Safety Report Follow-up#1 2003-BP-10569BP(1)	5/12/04	284	Initial Report	1/14/04
410	IND Safety Report Initial Report 2004-BP-02041BP(0) Initial Report 2004-BP-02715RA(0) Initial Report 2004-BP-03359BP(0)	5/12/04	N/A	N/A	N/A
411	• General Correspondence - Update to Pre-NDA Meeting Package	5/13/04	297 346	Request for Pre-NDA Meeting General Correspondence – Pre-NDA Meeting Package	1/30/04 3/17/04
412	• Information Amendment:Clinical Clinical Safety Information April Monthly report	5/14/04	N/A	Meeting w/FDA where BIPI agreed to submit for a period not less than 1 yr: all deaths for unrelated deaths as CIA cases, Grade 3 & 4 serious cases on a monthly basis, and a safety summary on a quarterly basis. (beginning on 1/19/04)	1/16/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
413	IND Safety Report Initial Report 2004-BP-03507BP(0)	5/14/04	N/A	N/A	N/A
414	General Correspondence Update to Analysis Proposal	5/14/04 4/15/04 4/22/04 4/30/04	N/A 384 392 400	Telefax from FDA Response to FDA Fax of 4/8/04:Preliminary Results from pharmacokinetic study 1182.51 Response to Request for Information: Tabular Listing of Deaths General Correspondence: Evaluation of Interactions w/ the agency regarding TPV Development program	4/8/04
415	IND Safety Report: Initial Report2004-BP-03519BP(0) Initial Report 2004-BP-01283BR(0)	5/17/04	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
416	2004-BP-03100MX(1)		N/A 280	Meeting between BI and FDA General Correspondence – Safety Information for January 16, 2004 Meeting to discuss adverse event information for tipranavir	1/16/04 1/12/04
417	IND Safety Report: Initial Report 2004-BP-01006BP(0)	5/18/04	N/A	N/A	N/A
418	Clinical Safety Information 2003-BP-10341AU(0) 2004-FF-00058FF(3)	5/18/04	N/A	Meeting between BI and FDA General Corr.– Safety Information for January 16, 2004 Mtg to discuss adverse event information for TPV	1/16/04 1/12/04
419	IND Safety Report: Initial Report 2004-FF-00264FF(0) Follow-up 2004-BP-03519BP(1)	5/19/04	N/A 415	N/A Initial report	N/A 5/17/04
420	Clinical Safety Information 2004-BP-02646BP(0) 2004-BP-02646BP(1) 2003-BP-1034AU(1)	5/19/04	N/A	Meeting between BI and FDA General Correspondence – Safety Information for January 16, 2004 Meeting to discuss adverse event information for tipranavir	1/16/04 1/12/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
421	IND Safety Report 2004-DE-02587DE(0) 2004-FF-00296FF(0)	5/20/04	 N/A N/A	 N/A N/A	 N/A N/A
422	IND Safety Report: Initial: 2004-FF-00284FF(0) Initial: 2004-FF-00297FF(0) Initial: 2003-DE-06173GB(0)	5/20/04	 N/A N/A N/A	 N/A N/A N/A	 N/A N/A N/A
423	IND Safety Report Clinical Safety Information 2003-FF-00508FF(2)	5/20/04	N/A	Meeting between BI and FDA General Correspondence – Safety Information for January 16, 2004 Meeting to discuss adverse event information for tipranavir	1/16/04 1/12/04
424	IND Safety Report: Initial Report: 2003-FF-00503FF(0)	5/20/04	N/A	N/A	
425	General Correspondence Update to pre-NDA meeting CTD-integrated analysis	5/21/04 N/A	346 N/A	Pre-NDA Meeting Package Pre-NDA Meeting Teleconference	3/17/2004 May 10, 2004
426	Information Amendment: Clinical Fatal Case Initial Report: 2004-BP-03659BP(0) Follow-up #1: 2004-BP-02543BP(1) Follow-up #4: 2004-UK-00030UK(4)	5/21/04	N/A	CIA Cases	
427	General Correspondence - Request for Teleconferenc-Update of Safety Reporting	5/21/04	369 N/A	General Correspondence - Teleconference with FDA	April 6, 2004 April 8, 2004

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	Procedures				
428	IND Safety Report Follow-up Report: 2004-BP-01006BP(1) Initial Report 2004BP-03620BP(0) Initial Report 2003-FF-00595FF(0)	5/21/04	417	Initial Report	5/18/04
429	IND Safety Report Initial Report: 2004-BP-03727BP(0)	5/21/04	N/A	N/A	N/A
430	IND Safety Report Follow-up: 2004-BP-03659BP(1)	5/24/04	426	Initial	5/21/04
431	2004-BP-03721BP(0)	5/24/04	N/A	N/A	N/A
432	IND Safety Report: 2004-BP-03640BP(0) 2004-BP-03614BR(0)	5/24/04	N/A	N/A	N/A
433	IND Safety Report: 2004-BP-03805BP(0)	5/26/04	N/A	N/A	N/A
434	IND Safety Report 2004-BP-03507BP(1) 2004-FF-00296FF(1)	5/26/04	413 421	Initial Initial	5/14/04 5/20/04
435	IND Safety Report 2004-BP-03359BP(1)	5/26/04	410	Initial	5/12/04
436	General Correspondence: Top Line Phase 3 RESIST Data	5/26/2004	N/A	Teleconference with Division	3/17/04 5/25/04
437	General Correspondence: Synopsis of Proposed Expanded Access Program - BIPI Trial 1182.70	5/26/2004	203 221 350 436	Draft Protocol Final Protocol 1182.58 Amendment 1 GC: Top Line Resist 1 and 2	1/23/03 4/3/03 3/19/04 4/27/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
438	Information Amendment: Clinical Fatal Cases 2004-FF-00180FF(1)	5/27/04	353	Initial	3/22/04
439	2004-BP-03519BP(2) 2004-BP-02706BP(2) 2004-BP-01283BR(1)	5/27/04	415 419 389 397 415	Initial Follow-up 1 Initial Follow-up 1 Initial	5/17/04 5/19/04 4/19/04 4/28/04 5/17/04
440	2004-BP-03727BP(1)	5/27/04	429	Initial	5/21/04
441	General Correspondence: Statistical Analysis Plan – submitting the summary of the RESIST protocol and amendments.	5/27/04	346	Pre-NDA Meeting Package	3/17/04
442	IND Safety Report 2004-BP-02414BP(0) 2004-BP-03928BP(0) 2004-BP-03862BP(0)	5/28/04	N/A N/A N/A	N/A N/A N/A	N/A N/A N/A
443	Information Amendment: Clinical U04-1256 (1182.11)	5/28/04	N/A	N/A	N/A
444	Information Amendment: Clinical Fatal Cases 2004-BP-03860BP(0)	5/28/04	N/A	7 Day Fax	5/24/04
445	Information Amendment Clinical Food Effect	5/28/04	N/A	request from T. Sinha requesting info on food effects on bioavail of SEDDS formul. in humans	5/27/04
446	Information Amendment: Clinical Bilirubin Lab Results	5/28/04	N/a	e-mail request from T. Sinha – requesting updated bilirubin data	5/27/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			375 401	for previous submissions • IND Safety Report Initial Report 2003-BP-03027BP(0) • IND Safety Report Follow-up 2003-BP-09788BR(3)	4/12/04 5/3/04
447	IND Safety Report Initial 2004-FF-00327FF(0) Initial 2004-FF-00315FF(0) Initial 2004-BP-03876AU(0)	5/28/04	N/A	N/A	
448	Information Amendment: CMC Request for Type A Meeting	5/28/04	N/A	N/A	
449	Information Amendment: Clinical Fatal Case 2004-DE-00489GB(0)	6/1/04	N/A	N/A	
450	IND Safety Reports Initial Reports 2004-FF-00321FF(0) 2004-FF-00326FF(0)	6/2/04	N/A	N/A	
451	Information Amendment: Clinical U03-3131-01 (1182.6) U04-3100 (1182.10) U04-3216 (1182.21):U03-3065-01 (1182.24)	6/3/04	N/A	N/A	

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
452	IND Safety Report: 2003-FF-00503FF(1) 2004-FF-00284FF(1) 2004-FF-00297FF(1)	6/3/04	424 422 422	Initial	5/20/04
453	Protocol Amendment: New Investigators 1182.58 Trial	6/4/04	N/A	N/A	
454	IND Safety Report 2004-FF-00026FF(1)	6/4/04	293	Initial	1/26/04
455	Information Amendment: Clinical 2004-NL-00039NL	6/7/04		Initial	
456	IND Safety Report: Follow-up 2003-FF-00595FF(1) 2003-FF-00640FF(3)	6/7/04	428 379 390	Initial Follow-up 1 Follow-up 2	5/21/04 4-13-04 4/20/04
457	IND Safety Report: Initial 2004-BP-04048BP(0) Initial 2004-BP-04071BP(0) Initial 2004-SW-00154DB(0)	6/7/04	N/A	N/A	N/A
458	IND Safety Report: Initial 2004-BP-04135BP(0) Initial 2004-BP-02885BP(0)	6/8/04	N/A	N/A	N/A
459	IND Safety Report: Follow-up 2003-DE-6173GB(1) Follow-up 2003-BP-09788BR(4)	6/9/04	422 267 271 275	Initial Initial Follow-up #1 Follow-up #2	5/20/04 12/1/03 12/19/03 12/31/03

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			401	Follow-up #3	5/3/04
	Follow-up 2004-DE-02587DE(1)		421	Initial	5/20/04
	Follow-up 2003-FF-00640FF(4)		284	Initial	1/14/04
			379	Follow-up #1	4/13/04
			390	Follow-up #2	4/20/04
			456	Follow-up #3	6/7/04
460	Information Amendment: CMC Type A IND Meeting Information Package for Oral Solution	6/11/04	448	A Type A "critical path" IND Meeting request	5/28/04
461	IND Safety Report:				
	Follow-up 2004BP-01006BP(2)	6/14/04	417	Initial	5/18/04
			428	Follow-up 1	5/21/04
462	Information Amendment: Clinical Safety Information May 1 Monthly report	6/14/04	N/A	Meeting w/FDA where BIPI agreed to submit for a period not less than 1 yr: all deaths for unrelated deaths as CIA cases, Grade 3 & 4 serious cases on a monthly basis, and a safety summary on a quarterly basis. (beginning on 1/19/04)	1/16/04
463	IND Safety Report Initial 2004-UK-00526UK(0)	6/15/04	N/A	7 Day Fax	6/10/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
464	IND Safety Report Follow-up 2004-BP-03727BP(2)	6/15/04	429 440	Initial Follow-up #1	5/21/04 5/27/04
465	IND Safety Report 2004-FF-00342FF(0)	6/15/04	N/A	N/A	N/A
466	IND Safety Report Follow-up 2003-BP-09788BR(5)	6/16/04	267 271 275 401 459	Initial Follow-up #1 Follow-up #2 Follow-up #3 Follow-up #4	12/1/03 12/19/03 12/31/03 5/3/04 6/9/04
467	Information Amendment: Clinical Safety 2004-BP-03659BP(2)	6/16/04	426 430	Initial Report Follow-up #1	5/21/04 5/24/04
468	IND Safety Report Initial 2003-FF-00532FF(0)	6/17/04	N/A	N/A	N/A
469	Information Response to FDA Request for Information – clarification regarding safety report case 2004-BP-02646BP(1) from trial 1182.12	6/17/04	N/A	Teleconference between BI and Division	6/7/04
470	Information Amendment:PharmTox 24- Month oral Rat Carcinogenicity Study	6/17/04	151	Draft Protocol Submitted	5/24/02
471	General Correspondence – Request for FDA Feedback – Request for Telecon – Amendment to NDA Electronic Submission	6/18/04	346 N/A	Electronic submission proposal Pre-NDA telecon and meeting	3/17/04 5/10/04 & 6/2/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
				Informal e-mail from J. Liang	6/14/04
472	IND Safety Report: Follow-up 2004-BP-03876AU(1)	6/18/04	447	Initial	5/28/04
473	IND Safety Report Initial 2004-BP-04375BP(0)	6/18/04	N/A	N/A	N/A
474	Information Amendment: Pharmacology/Toxicology U04-3111 U04-3178 Request for FDA Feedback	6/21/04	318	GC: Request for FDA Feedback on Immunotox Proposal FDA Response FAX	2/20/04 5/18/04
475	IND Safety Report Follow-up 2004-BP-03614BR(1)	6/21/04	432	Initial	5/24/04
476	IND Safety Report Initial 2004-BP-04465BP(0)	6/21/04	N/A	N/A	N/A
477	Amendment to Information Package for Type A Meeting: CMC	6/21/04	448 460	Type A "critical path" IND Meeting request Information Amendment: CMC Type A IND Meeting Information Package for Oral Solution	May 28, 2004 June 11, 2004

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478	IND Safety Report Initial 2004-BP-04500RA(0)	6/21/04	N/A	N/A	N/A
479	IND Safety Report Initial 2004-FF-00364FF(0) Follow-up 2004-BP-03862BP(1)	6/22/04	 N/A 442	 N/A Initial	 N/A 5/28/04
480	IND Safety Report: Follow-up 2004-BP-02715RA(1)	6/22/04	 410	 Initial	 5/12/04
481	IND Safety Report Initial 2004-FF-00355FF(0) Initial 2004-BP-04612BP(0)	6/22/04	N/A N/A	N/A N/A	N/A N/A
482	IND Safety Report Initial 2004-SW-00154DB(0)	6/22/04	N/A	N/A	N/A
483	Type A IND Meeting-Response to FDA Pre-Meeting Request for Information-CMC-Tipranavir Oral Solution	6/22/04	 260	Facsimile correspondence from Ms. Tanima Sinha Information Amendment	5/22/04 10/29/03
483a	IND Safety Report Follow-up 2004-SW-00154DB(1)	6/23/04	457	Initial	6/7/04
484	IND Safety Report Initial 2004-BP-04608BP(0)	6/23/04	N/A	N/A	N/A
485	IND Safety Report Follow-up 2004-ES-00091ES(1) Follow-up 2004-FF-00315FF(1) Follow-up 2004-FF-00326FF(1) Follow-up 2003-FF-00595FF(2)	6/23/04	 403 447 450 428 456	 Initial Initial Initial Initial Follow-up #1	 5/4/04 5/28/04 6/2/04 5/21/04 6/7/04

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486	IND Safety Report Initial 2004-FF-00361FF(0)	6/24/04	N/A	N/A	N/A
487	IND Safety Report Initial 2004-BP-04794BP(0)	6/25/04	N/A	N/A	N/A
488	Information Amendment: Pharmacology/Toxicology U04-3184	6/25/04	N/A	N/A	
489	IND Safety Report Initial 2003-FF-00569FF(0)	6/25/04	N/A	N/A	N/A
490	IND Safety Report Follow-up 2004-FF-00321FF(1)	6/25/04	450	Initial	6/2/04
491	IND Safety Report Follow-up 2004-FF-00117FF(2)	6/25/04	326 407	Initial Follow-up #1	3/1/04 5/10/04
492	IND Safety Report Initial 2004-BP-04724BP(0) Initial 2004-FF-00372FF(0) Follow-up 2003-FF-00508FF(3)	6/25/04	N/A N/A 284 373 423	N/A N/A Initial Follow-up#1 Follow-up#2	N/A N/A 1/14/04 4/9/04 5/20/04
493	IND Safety Report Initial 2004-FF-00371FF(0) Initial 2004-FF-00373FF(0)	6/28/2004	NA	NA	NA
494	IND Safety Report Initial 2004-BP-04770BR(0)	6/28/2004	N/A	N/A	N/A

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
495	IND Safety Report Initial Report: 2004-BP-04688BR(0)	6/28/2004	NA	NA	NA
496	Information Amendment:Clinical Step 1 of Drug Interaction Analysis (SN 414) Request for Teleconference	6/29/04	384	Response to FDA Request for Information	4/15/04
			392	Response to Request for Information: Tabular Listing of Deaths	4/22/04
			400	General Correspondence: Evaluation of Interactions w/ the agency regarding TPV Development program	4/30/04
			414	General Correspondence:Update to Analysis Proposal	5/14/04
			N/A	Telefax from FDA	6/8/2004

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
497	IND safety report Follow-up 2004-FF-00355FF(1)	6/29/2004	481	Initial	6/22/04
498	Protocol Amendment Change in Protocol Amendment 5 and 6 1182.12	6/30/2004	205 214 220 230	New Protocol 1182.12 Amendments 1 &2 Amendment 3 Amendment 4	2/4/2002 3/19/2002 3/31/2002 6/10/2003
499	General Correspondence; BIPI Meeting Minutes of June 7, 2004 – safety reporting processes and procedures.	6/30/04	N/A	June 7, 2004 Meeting	N/A
500	IND Safety Report Initial 2004-CN-00238CN(0) Initial 2004-IT-00093IT(0)	6/30/04	N/A	N/A	N/A
501	General Correspondence/Request for FDA Feedback/Request for Teleconference NDA Clinical Summary Cross Referencing Plan, Presentation of Patient Disposition, Clinical Summary Integration Plan.	7/1/04	N/A N/A N/A 521	Pre NDA Meeting with FDA Pre-NDA Meeting with FDA Teleconference with Ms. Sinha, FDA Project Manager Pre-NDA Meeting Minutes	May 10, 2004 June 2, 2004 June 28, 2004 July 19, 2004
502	IND Safety Report Follow-up 2004-UK-00526UK(1)	7/1/04	463	Initial	6/15/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
503	IND Safety Report Initial 2004-FF-00149FF(0)	7/1/04	N/A	N//A	N/A
504	IND Safety Report Initial 2004-UK-00597UK(0)	7/2/04	7/2/04	N/A	N/A
505	IND Safety Report Follow-up 2004-FF-00026FF(2) Follow-up 2004-FF-00180FF(2) Initial 2004-BP-04910BP(0)	7/2/04	293 454 353 438 N/A	Initial Follow-up #1 Initial Follow-up #1 N/A	1/26/04 6/4/04 3/22/04 5/27/04 N/A
506	IND Safety Report Initial: 2004-FF-00401FF(0) Initial: 2004-UK-00320UK(1) Initial: 2004-BP-04967BP(0)	7/2/04	N/A	N/A	2004-UK-00320UK(1) is initial. Incorrectly labeled follow-up 1
507	IND Safety Report Follow-up 2004-UK-00030UK(5) Follow-up 2003-FF-00503FF(2)	7/6/04	289 289 298 298 426 424 452	Initial Follow-up #1 Follow-up #2 Follow-up #3 Follow-up #4 Initial Follow-up #1	1/20/04 1/20/04 2/2/04 2/2/04 5/21/04 5/20/04 6/3/04
508	General Correspondence Proposed Expanded Access Program BIPI Trial 1182.70	7/7/04	437	General Correspondence draft protocol synopsis	5/26/04
509	Protocol Amendment New Investigator 1182.17	7/7/04	078 113	Protocol 1182.17 PA Dr. Coleen Tutton	2/12/2001 8/29/2001

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
510	IND Safety Report Follow-up 2004-BP-04688BR(1) Initial 2004-BP-05113MX(0)	7/9/04	 495 N/A	 Initial N/A	 6/28/04 N/A
511	IND Safety Report Follow-up 2004-03862BP(2) Follow-up 2004-BP-04724BP(1) Follow-up 2004-FF-00342FF(1)	7/12/04	 442 479 492 465	 Initial Follow-up #1 Initial Initial	 5/28/04 6/22/04 6/25/04 6/15/04
512	Protocol Amendment New Investigator 1182.58	7/12/04	221	Protocol 1182.58 original submission	4/3/03
513	Response to FDA Request for Information Response to Telefax from FDA, Anthony ElHage – Requesting info on investigators, sites, discont. and reasons discont. for all of the pivotal sites for TPV Trials (1182.12, 1182.48 and 1182.14)	7/12/04	N/A	Telefax from FDA, Anthony ElHage – Requesting info on investigators and sites for the pivotal sites for TPV.	6/3/04
514	U04-3257 Toxicokinetic of Tipranavir in a 13-week oral toxicity study in rats.	7/12/04	N/A		
515	IND Safety Report Follow-up: 2003-BP-09788BR(6)	7/13/04	 267 271 275 401 459	 Initial Follow-up #1 Follow-up #2 Follow-up #3 Follow-up #4	 12/01/03 12/19/03 12/31/03 5/03/04 6/09/04

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	Follow-up: 2004-BP-04612BP(1) Initial: 2004-BP-05320BP(0) Follow-up: 2004-FF-00026FF(3)		466 481 N/A 293 454 505	Follow-up #5 Initial N/A Initial Follow-up #1 Follow-up #2	6/16/04 6/22/04 N/A 1/26/04 6/04/04 7/02/04
516	Information Amendment: Clinical (U03-3605-01 & U04-3198)	7/13/04	N/A	N/A	N/A
517	Information Amendment: Clinical-Safety Information-Jun 2004 Monthly Report	7/14/04	N/A	Meeting w/FDA where BIPI agreed to submit for a period not less than 1 yr: Grade 3 & 4 serious cases on a monthly basis. (beginning on 1/19/04)	N/A
518	IND Safety Report Initial: 2004-DE-03659DE(0) Initial: 2004-FF-00410FF(0) Follow-up:2004-FF-00373FF(1) Follow-up: 2004-UK-00526UK(2) Follow-up: 2004-BP-02715RA(2)	7/14/04	 N/A N/A 493 463 502 410 480	 N/A N/A Initial Initial Follow-up #1 Initial Follow-up #1	 N/A N/A 6/28/04 6/15/04 7/01/04 5/12/04 6/22/04
519	IND Safety Report Initial: 2004-BP-05348BR(0) Initial: 2004-BP-05301RA(0)	7/15/04	N/A	N/A	N/A

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520	IND Safety Report 2004-CN-00253CN(0)	7/16/04	N/A	N/A	N/A
521	General Correspondence: Pre-NDA Meeting Minutes	7/19/04	N/A	Meeting with FDA (Pre-NDA)	6/2/04
522	General Correspondence: Request for FDA Feedback Point of discussion in telecon was the difference between "end-of-text" tables (Section 15 of reports) and appendices (Appendix 16.1.9.2, referred to as STATDOCS). Submission of examples of these tables and appendices to illustrate the content of the displays and their supportive statistical documentation	7/20/04	N/A	teleconference	7/12/04
523	General Correspondence: Step 1 of Drug Interaction Analysis In preparation for our teleconference with Division t July 21, 2004, a clear tabular representation of the drugs proposed for study in Step 2 of our analysis plan	7/20/04	496	submission provided a descriptive analysis of concomitant medications used in HIV-1 patients who have died during tipranavir studies or have had clinical progression events in the two ongoing RESIST trials (*Step 1 of the Drug Interaction Analysis Plan*	6/29/04
524	IND Safety Report Follow-up: 2004-UK-00597UK(1) Initial: 2004-BL-00130BL(0)	7/20/04	 504 N/A	 Initial N/A	 7/02/04 N/A

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525	IND Safety Report Follow-up: 2004-FF-00327FF(1) Follow-up: 2004-BP-04724BP(2)	7/21/04	 447 492 511	 Initial Initial Follow-up #1	 5/28/04 6/25/04 7/12/04
526	Information Amendment Clinical Reports (U04-3248, U04-3259)	7/22/04	N/A	N/A	N/A
527	Information Amendment: Pharmacology/Toxicology (U03-3565, U03-3153)	7/22/04	N/A	N/A	N/A
528	IND Safety Report Follow-up: 2004-FF-00410FF(1) Follow-up: 2004-FF-00256FF(1)	7/22/04	 518 393	 Initial Initial	 7/14/04 4/26/04
529	IND Safety Report Initial: 2004-DE-03872DE(0) Initial: 2004-BP-05611BP(0)	7/23/04	N/A	N/A	N/A
530	IND Safety Report: Initial: 2004-CN-00263CN(0)	7/26/04	N/A	N/A	N/A
531	IND Safety Report Follow-up: 2004-DE-03659DE(1)	7/27/04	 518	 Initial	 7/14/04
532	IND Safety Report Initial report: 2004-BP-05700BP(0) Follow-up #2: 2004-UK-00597UK(2)	7/28/04	 504 524	 Initial Initial Follow-up#1	 7/2/04 7/20/04

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	Follow-up #1: 2004-BP-04048BP(1) Follow-up #3: 2004-BP-04724BP(3)		457 492 511 525	Initial Initial Follow-up#1 Follow-up#2	6/7/04 6/25/04 7/12/04 7/21/04
533	General Correspondence: Request for FDA Feedback - Resistance Template	7/28/04	N/A N/A	Pre-NDA Meeting FDA email providing an updated template for reporting resistance data in the TPV NDA	6/2/2004 6/29/2004
534	Response to FDA Request for Information – In Vitrol No. 527. BI would like to request feedback on the proposal for design and timing for further study of approved ARV compounds	7/28/04	N/A N/A\ SN 123 SN 213 N/A	Type C Clinical Development Meeting between FDA and BI (FDA minutes issued Nov 30, 2001 BI minutes Early data submission Telefax from FDA	10/5/01 11/30/01 11/7/01 3/18/03 11/18/03
535	Response to FDA Request for Information - Analysis Plan for Step 2 Cohort Analysis	7/28/04	414 N/A	Planned Cohort Analysis Proposal Teleconference	5/14/04 7/21/04

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	Aanalysis plan describing the planned cohort analysis proposed in BI is actively proceeding with this cohort analysis				
536	Response to FDA Request for Information: General Global Expanded Access Overview	7/28/04	508 N/A	Draft EAP protocol Telecon w/FDA requesting EAP overview	7/7/04 7/14/04
537	IND Safety Report Initial 2004-BP-05731BP(0) Initial: 2004-DE-03306DE(0)	7/29/04	N/A	N/A	N/A
538	Information Amendment: Clinical-Safety Information-July 2004 Quarterly Safety Summary	7/30/04	N/A	Meeting w/FDA where BIPI agreed to submit for a period not less than 1 yr: Grade 3 & 4 serious cases on a monthly basis, and a safety summary on a quarterly basis. (beginning on 1/19/04)	
539	IND Safety Report Initial: 2004-BP-05812BP(0) Initial: 2004-IT-00118IT(0) Follow-up#1: 2004-CN-00253CN(1)	7/30/04	NA NA 520	Initial Report	7/16/04
540	IND Safety Report 2004-SW-00232DB(0) 2004-BP-05611BP(1) 2004-BP-04724BP(4)	8/3/04	N/A 529 492	N/A Initial Initial	N/A 7/23/04 6/25/04

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	2004-FF-00234FF(1)		511 525 532 387	Follow-up #1 Follow-up #2 Follow-up #3 Initial	7/12/04 7/21/04 7/28/04 4/16/04
541	IND Safety Report Initial 2004-BP-06047BP(0) Initial 2004-FF-00440FF(0)	8/4/04	 N/A N/A	 N/A N/A	 N/A N/A
542	IND Safety Report Initial 2004-BP-06030BP(0)	8/4/04	 N/A	 N/A	 N/A
543	IND Safety Report Initial: 2004-BP-05975BP(0) Follow-up #1: 2004-BP-05731BP(1)	8/5/04	 N/A 537	 N/A Initial	 N/A 7/29/04
544	IND Safety Report Initial: 2004-BP-05944BP(0) Initial: 2004-BP-05859BP(0)	8/5/04	 N/A N/A	 N/A N/A	 N/A N/A
545	Information Amendment:Pharmacology/Toxicology (U04-3154, U04-3179, U04-3309, (U04-3232)	8/6/04	N/A	N/A	N/A
546	IND Safety Report Corrected Information for Initial Report: 2004-BP-05859BP(0)	8/6/04	544	Initial Report	8/5/04

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547	IND Safety reports Initial: 2004-BP-06139BP(0) Initial: 2004-BP-06185BP(0) Follow-up: 2004-BP-05320BP(1) Follow-up: 2004-BP-05700BP(1)	8/6/04	 N/A N/A 515 532	 N/A N/A Initial Initial	 N/A N/A 7/13/04 7/28/04
548	IND Safety Report Initial: 2004-FF-00101FF(0) Initial: 2004-FF-00256FF(0) Initial: 2003-BP-02917BP(0) Initial: 2004-BP-06221BP(0) Initial: 2004-DE-04165DE Follow-up: 2004-FF-00284FF(2) Follow-up: 2004-BP-04375BP(1)	8/9/04	 422 452 473	 Initial Follow-up #1 Initial	 5/20/04 6/3/04 6/18/04
549	Protocol Amendment: 1182.14 (Amendment #3 dated June 22, 2004)	8/9/2004	244 306	Original protocol Amendments 1 and 2	8/8/2003 2/6/2004
550	IND Safety Report Corrected Information for Initial Report 2004-FF-00265FF(0)	8/10/04	 548	 Wrong CIOMS (2004-FF-00256FF(0) was attached	 8/9/04
551	IND Safety Report Initial: 2004-BP-06076BP(0) Follow-up: 2004-BP-05320BP(1)	8/10/04	 N/A 515	 7 Day Fax was sent on 8/2/04 Initial	 7/13/04

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552	IND Safety Report Initial: 2004-FF-00459FF(0)	8/11/04	NA	N/A	N/A
553	IND Safety Report 2004-BP-04927BR(0) 2004-BL-00137BL(0)	8/12/2004	N/A	N/A	N/A
554	Information Amendment: Pre-Clinical Toxicology Reports U00-3087 and U00-0389	8/12/2004	N/A	N/A	N/A
No SN	IND Safety Report 7--DAY FAX 2004-DE-04275DE(0)	8/12/2004	N/A	N/A	N/A
555	IND Safety Report Initial: 2004-BP-06314BP(0)	8/12/04	N/A	N/A	N/A
556	Information Amendment: Clinical-Safety Information-July 2004 Monthly Report	8/13/04	N/A	N/A	N/A
557	IND Safety Reports Initial: 2004-BP-02018BP(0)	8/13/04	N/A	N/A	N/A
558	IND Safety Report Follow-up: 2003-BP-10942BP(3)	8/16/04	281 323 360	Initial Follow-up #1 Follow-up #2	1/12/04 2/27/04 3/26/04
559	IND Safety Report Initial: 2004-BP-06423BR(0)	8/16/04	N/A	N/A	N/A

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560	IND Safety Report Initial: 2004-DE-04275DE(0)	8/17/04	N/A	7 Day Fax	8/12/04
561	IND Safety Report Follow-up: 2004-BP-05731BP(2)	8/18/04	 537 543	 Initial Follow-up #1	 7/29/04 8/5/04
562	IND Safety Report Initial: 2004-CN-00285CN(0) Follow-up: 2004-UK-00057UK(4)	8/19/04	N/A 296 313 329 341	N/A Initial Follow-up #1 Follow-up #2 Follow-up #3	N/A 1/30/04 2/13/04 3/5/04 3/15/04
563	General Correspondence: Letter of Authorization for Emergency Treatment Dr. Gregory Storch	8/20/04	N/A	N/A	N/A
564	IA Clinical Reports 1182 .37, 1182.4, 1182.41	8/20/04	N/A	N/A	N/A
565	IND Safety Report Initial: 2004-FF-00068FF(0) Follow-up: 2004-FF-00440FF(1)	8/20/04	 N/A 541	 N/A Initial	 N/A 8/4/04
566	Information Amendment: Clinical (Final Draft Clinical Report: 1182.51)	8/23/04	N/A	N/A	N/A
567	IND Safety Report Initial: 2004-NL-00113NL(0)	8/23/04	N/A	N/A	N/A

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568	IND Safety Report Follow-up: 2004-FF-00364FF(1) Follow-up: 2004-BP-05731BP(3)	8/24/04	 479 537 543 561	 Initial Initial Follow-up #1 Follow-up #2	 6/22/04 7/29/04 8/5/04 8/18/04
569	IND Safety Report Initial: 2004-BP-07028BP(0) Initial: 2004-BP-06866MX(0) Initial: 2004-FF-00482FF(0)	8/25/04	N/A	N/A	N/A
570	Response to FDA Request for Information: Resistance Template (FDA 20 August, 2004 Fax) (CD w/datasets provided)	8/25/04	SN 533	Template for reporting resistance data in the TPV NDA	7/28/04
571	IND Safety Report Follow-up: 2004-BP-06047BP(1)	8/26/04	 541	 Initial	 8/4/04
572	IND Safety Report Follow-up: 2004-DE-04275DE(1) Initial: 2003-FF-0011FF(0)	8/27/04	 560 N/A	 7 Day Fax Initial N/A	 8/12/04 8/17/04 N/A
573	IND Safety Report Initial: 2003-FF-00618FF(0) Follow-up: 2004-FF-00410FF(2)	8/27/04	N/A 518 528	N/A Initial Follow-up #1	N/A 7/14/04 7/22/04
574	IND Safety Report Initial Report: 2004-FF-00491FF(0) Follow-up: 2004-BP-05812BP(1) Follow-up: 2004-BP-03787BP(1)	8/30/2004	 539 433	 Initial Initial	 7/30/2004 5/26/2004

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	Follow-up #4: 2004-BP-00114BP(4)		288 308 359 382	Initial Follow-up #1 Follow-up#2 Follow-up#3	1/20/2004 2/9/2004 3/24/2004 4/14/2004
FAX	IND 7-Day phone fax 2004-BP-07145BP	8/31/2004	N/A	N/A	N/A
575	IND Safety Report Follow-up Report: 2004-BP-06030BP(1)	8/31/2004	542	Initial	8/4/2004
576	IND Safety Report Initial: 2004-CN-00295CN(0)	9/1/2004	N/A	N/A	N/A
FAX	IND 7-Day phone fax 2004-BP-03153BR	9/3/2004	N/A	N/A	N/A
577	Information Amendment:Clinical Final Draft Protocol 1182.60	9/10/04	N/A	N/A	N/A
578	IND Information Amendment Clinical – Safety Information – August 2004 Monthly Report	9/15/04	N/A	N/A	N/A
579	IND Safety Reports (September 1-15, 2004)	9/15/04	N/A	N/A	N/A
580	Protocol Amendment: New Investigators 182.58	9/23/04	N/A	N/A	N/A
581	Response to FDA Request for Information: Site Information on Trials 1182.12; 1182.48; 1182.14	9/23/04	N/A 513	Telefax from FDA requesting a list of all investigators, sites, pt numbers, discontinuations for pivotal clinical trials Submission of req listing above.	6/3/04 7/12/04

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582	Information Amendment: Pharmacology/Toxicology Request for Feedback on Study of Immunotoxicity requested by FDA on August 30, 2004	9/23/04	318 N/A	Outline of immunotoxicity Program Teleconference discussion of immunotox program	2/20/04 8/30/04
583	General Correspondence: eSubmission Demonstration	9/27/04	NA	Teleconference confirming TPV electronic submission demo scheduled for 10/05/05	9/3/04
584	General Correspondence: Request for Evaluation of Tradenames	9/30/04 N/A	307 N/A	Request for Evaluation of Tradenames-VRAY, ELODIUS, ONTINOR e-mail to Tanima Sinha requesting a delay in the review of TPV tradename pending internal decisions on a potential new tradename	2/6/04 6/30/04
585	IND Safety Reports (September 16-30, 2004)	9/30/04	N/A	N/A	N/A
586	Info amendment: Clinical- Cohort Analysis of Concomitant Medications a report summarizing the results of special	10/1/04	535	Submission of details of proposed cohort analysis.	7/28/04

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	cohort analysis	535	414	First described cohort analysis.	5/14/04
587	Information Amendment: Pharmacology/Toxicology and Clinical (ECG Rpt U04-3310 and interim CTR 1182.17, U04-3360)	10/7/2004	N/A	N/A	N/A
588	Protocol Amendment: New Investigators: 1182.17 & 1182.58	10/7/2004	N/A	N/A	N/A
589	Information Amendment: Clinical-Safety Information-September 2004 Monthly Report	10/13/04	N/A	N/A	N/A
590	Proposed Changes in Written Request for Pediatric Studies	10/14/04	186 N/A 242 N/A	Pediatric Proposal Pediatric Written Request Changes to Written Request Teleconference	11/15/02 1/22/03 7/23/03 10/02/03
591	IND Safety Reports (October 1-15, 2004)	10/15/04	N/A	N/A	N/A
FAX	IND Safety Report: 7-Day Facsimile 2004-BP-09458BP(0)	10/15/04	N/A	N/A	N/A
FAX	IND Safety Report: 7 -Day Facsimile 2004-BP-09805BP(0)	10/20/04	N/A	N/A	N/A
592	Protocol Amendment: Change in Protocol 1182.17 Amendment 6	10/21/04	078 101 154 222	Original Protocol Amendment 1 Amendment 2 Amendment 3	2/12/01 6/25/01 6/12/02 4/22/03

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			247 404	Amendment 4 Amendment 5	9/4/03 5/5/04
593	IND Safety Reports (October 16-30, 2004)	10/28/04	N/A	N/A	N/A
594	Investigators Brochure Version 8	11/1/04	146 210 386	Information Amendment - Clinical Updated Investigators Brochure Version 5 Information Amendment – Clinical Updated Investigators Brochure Version 6 Information Amendment – Clinical Updated Investigators Brochure Version 7	4/26/02 2/25/03 4/16/04
595	Protocol Amendment New Investigator New Investigators: 1182.17 & 1182.58	11/3/2004	N/A	N/A	N/A
none	IND Safety Report 7 day Fax 2004-CN-00399CN(0)	11/12/2004	11/12/2004	N/A	N/A
596	IND Safety Reports (November 1-15, 2004)	11/15/04	N/A	N/A	N/A
597	General Correspondence LOA for Emergency USE	11/15/04	11/15/04	N/A	N/A
598	Monthly Safety Report October 1- 31	11/15/04	11/15/04	N/A	N/A

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599	General Correspondence – Emergency Use Authorization – Dr. Meislich	11/16/04	11/16/04	N/A	N/A
600	IND ANNUAL REPORT PROPOSAL TIMELINE	11/18/04	N/A 521 N/A	Meeting between BIPI and Division BI meeting minutes FDA meeting minutes	6/2/04 7/109/04 11/09/04
601	IND Safety Reports (November 16-30, 2004)	11/30/04	N/A	N/A	N/A
602	Information Amendment: Clinical-Safety Information-November 2004 Monthly Report	12/13/04	N/A	N/A	N/A
603	Information Amendment: Clinical: Updated Investigator's Brochure Version 9 Response to Dr. James comments on the IDB submitted 11/1/04 with updates to the IDB	12/13/04	146 210 386	Information Amendment - Clinical Updated Investigators Brochure Version 5 Information Amendment – Clinical Updated Investigators Brochure Version 6 Information Amendment – Clinical Updated Investigators Brochure Version 7	4/26/02 2/25/03 4/16/04

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			594 N/A	Updated Investigators Brochure – Version 8 Telefax from Dr. James Commenting on the updated IB submitted on 11/1/04	11/1/04 11/5/04
604	IND Safety Reports (December 1-15, 2004)	12/15/04	N/A	N/A	N/A
605	IND Safety Reports (December 15-30, 2004)	12/30/04	N/A	N/A	N/A
606	Information Amendment: Pharmacology/Toxicology study summary of unaudited draft results of the immunotoxicity study to NDA 21-814 (Amendment 017; January 4, 2005).	1/04/05	318 N/A	Plans for immunotoxicity testing for TPV Teleconference	2/20/04 9/17/04
607	Information Amendment: CMC provide updated CMC documentation for the oral solution drug product to support on-going and future clinical trials	12/14/04	244 306 549	Pediatric Protocol - 1182.14 Amendments 1 and 2 Amendment 3	8/8/03 2/6/04 8/9/04
608	Information Amendment: Clinical-Safety Information-December 2004 Monthly Report	1/10/05	1/13/05	N/A	N/A
FAX	IND 7 Day Fax 2005-BP-00186BP(0)	1/13/05	N/A	N/A	N/A
FAX	IND 7 Day Fax 2005-BP-00303BP(0)	1/14/05	N/A	N/A	N/A

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609	IND Safety Reports (January 1-15, 2005)	1/14/05	1/14/05	N/A	N/A
610	IND Protocol Amendment New Investigators 1182.17 & 1182.58	1/21/05	1/21/05	N/A	N/A
611	In vitro - virologic interactions *in vitro* virologic interactions study (report U04-3529).	1/21/05	N/A 534 N/A	Pre-NDA meeting held on June 2, 2004. Submission requesting feedback on study design FDAs response to 7/28/04 submission	N/A 7/28/04 8/12/04
612	IND Safety Reports (January 17-31, 2005)	1/31/05	N/A	N/A	N/A
FAX	IND 7 Day Fax 2005-BP-01108BP(0)	2/1/05	N/A	N/A	N/A
FAX	IND 7 Day Fax 2005-bp-01631BP(0)	2/10/05	N/A/	N/A	N/A
613	Information Amendment: Clinical Version 3 of trial 1182.52 report (U03-3236-03) antiretroviral drug-experienced subjects. Content not changed, just minor formatting.	2/11/05	N/A	Original NDA	10/21/04
FAX	IND 7 Day Fax 2005-BP-01868AU(0)	2/14/05	N/A	N/A	N/A
614	IND Safety Reports (Feb. 1-15, 2005)	2/15/05	N/A	N/A	N/A
615	Monthly Report (Feb. 15, 2005)	2/15/05	N/A	N/A	N/A
616	IND Safety Reports Vital Status cases (February 1-15, 2005)	2/15/05	N/A	N/A	N/A
617	IND ANNUAL REPORT	2/22/05	N/A	N/A	N/A

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618	Information Amendment: Pharm/Tox - mouse carcinogenicity study arm termination – request for FDA feedback	2/23/05	151	Draft Protocol (special protocol assessment)	5/24/02
619	Letter of authorization – Glaxo Smith Kline for protocol GW873140 for IND 65238 .	2/25/05	N/A	N/A	N/A
620	IND Safety Reports (February 16-28, 2005)	2/28/05	N/A	N/A	N/A
621	Information Amendment: Pharm/Tox immuno toxicity report U05-3021	3/3/05	SN 318	Overview of Immunotoxicity program	2/20/04
			Teleconference	Discussion of immunotox program	8/30/04
			SN 582	Request for feedback on the adequacy of protocol designed for the immunotox study and the planned submission timeline	9/23/04
			A017	Summary of U05-3021	1/4/05
622	Protocol Amendment: Change in Protocol Amendments 7 & 8 to 1182.12 Trial	3/3/05	186	End of Phase II Background Document	11/15/02

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Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
			205 214 220 230 498	Original Protocol Amendments 1and 2 Amendment 3 Amendment 4 Amendment 5 & 6	2/4/03 3/19/03 3/31/03 6/10/03 6/30/04
FAX	IND 7 Day Fax 2005-BP-03684BP(0)	3/10/05	N/A	N/A	N/A
623	Protocol Amendment: Change in Protocol 1182.14 - Amendments 4 & 5	3/10/05	244 306 549	Original protocol Amendments 1 and 2 Amendment 3	8/8/2003 2/6/2004 8/9/2004
FAX	IND 7 Day Fax 2005-BP-03525BP(0)	3/11/05	N/A	N/A	N/A
FAX	IND 7 Day Fax 2005-BP-01732BR(0)	3/14/05	N/A	N/A	N/A
624	Monthly Report (March 15, 2005)	3/15/05	N/A	N/A	N/A
625	IND Safety Reports (March 1-15, 2005)	3/15/05	N/A	N/A	N/A
FAX	IND 7 Day Fax 2005-DE-00654DE(0)	3/17/200	N/A	N/A	N/A
626	Information Amendment - Clinical (Microbiology) Tipranavir Resistance Report (U04-3215), to describe the emergent resistance data	3/25/05	A029 A030	2 Month Safety Update Amendment to NDA 21814	2/22/05 2/23/05
FAX	IND 7 Day Fax 2005-IT-0053IT(0)	3/28/05	N/A	N/A	N/A
627	Information Amendment – Pharmacology/Toxicolgy	3/31/05	N/A	N/A	N/A

Tipranavir Serial Number Log

Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
	U02-3410, U03-3059, U03-3060, U03-3061, U03-3080, U03-3086, U03-3193, U03-3213, U03-3213, U03-3288, U03-3289, U03-3576, U03-3578, U03-3583, U04-3006, U04-3028, U04-3030, U04-3084, U04-3101, U04-3102, U04-3110, U04-3112, U04-3132, U04-3183, U04-3233, U04-3234, U04-3307, U04-3371, U04-3372, U04-3406, U04-3529				
628	IND Safety Reports (March 16-31, 2005)	3/31/05	N/A	N/A	N/A
629	Information Amendment: Pharmacology/Toxicology U04-3531 Tipranavir: Assessment of Testicular Histopathologic Findings in Toxicity	3/31/05	N/A	N/A	N/A
630	IND Safety Report: 2005-BL-00074BL(0) One pg inadvertently left out of batch submission	4/1/05	628	Batched Submission	3/31/05
631	INFORMATION AMENDMENT;PK RESPONSE TO BILR STUDY Drug-Drug Interaction study between BILR355 and TPV being discontinued	4/4/05	N/A	N/A	N/A
FAX	IND 7 Day Fax 2005-BP-05595BR(0)	4/12/05	N/A	N/A	N/A

Tipranavir Serial Number Log

Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
632	IND Safety Reports (Apr 1-15, 2005)	4/15/05	N/A	N/A	N/A
633	General Correspondence(LOA Emergency Use – Dr. Ricaurte	4/18/2005	N/A	N/A	N/A
FAX	IND 7 Day Fax 2005-UK-00633UK(0)	4/22/05	NA	N/A	N/A
634	Protocol Amendment:New Protocol :Change in protocol - 1182.93 bioequivalence study submission of original protocol and Amendment 1	4/27/05	N/A	N/A	N/A
635	Information Amendment CMC information for the drug products to be used in clinical trial 1182.93. This trial is being conducted to establish bioequivalence between 2 batches of Tipranavir Capsules 250 mg maintained under different storage conditions.	4/28/05	N/A	N/A	N/A
636	IND Safety Reports (April 16-29, 2005)	5/03/05	N/A	NA	N/A

Tipranavir Serial Number Log

Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
637	Information Amendment/Pharmacology Toxicology Mouse Carcinogenicity Study Arm Termination	5/3/05	151 618	Survival mouse carcinogenicity study Early termination proposal	5/24/02 2/23/05
638	Letter of Authorization in support of drug interaction study of Tipranavir and Reverset in healthy subjects by Incyte corporation	5/4/05	N/A	N/A	N/A
639	Information Amendment/Pharmacology U05-3043, U05-3045 – Antiviral Activity Reports	5/6/05	N/A	N/A	N/A
640	Response to FDA Request for Information Please reference Ms. Sinha's March 16, 2005 e-mail query with comments regarding updating our drug metabolism and drug interaction information in our Investigators Brochure (IB) and Emergency Access Protocol- submission of DRAFT letter to investigators	5/13/05	e-mail teleconference	e-mail query regarding updating the IB and Emergency Access Protocol for drug metabolism and drug interaction information. Agreement to inform investigators of updated info via letter rather than updating IB and EAP.	3/16/05 4/27/05
641	IND Safety Reports (May 1 – 15, 2005)	5/18/05	N/A	N/A	N/A
642	General Correspondence - Letter or Authorization for Emergency Use Dr. Mael	5/26/05	N/A	N/A	N/A

Tipranavir Serial Number Log

Serial No	Description of Submission	Date of Submission	Serial No. Referenced	Description of Reference	Date of Reference
643	IND Safety Reports (May 16-31, 2005)	6/3/05	N/A	N/A	N/A
644	IND Safety Reports (June 1-15, 2005)	6/17/05	N/A	N/A	N/A
FAX	7 day fax case 2005-BP-1014BP	6/27/05	N/A	N/A	N/A
FAX	7-day fax case 2005-ES-00183ES	6/27/05	N/A	N/A	N/A
645	IND Safety Reports (June 16-30, 2005)	7/1/05	N/A	N/A	N/A
646	Information Amendment:Clinical: New Protocols: Request for FDA Feedback (Post-Marketing Commitments)	7/13/05	A080 NDA 21-814	Post marketing study commitments	6/21/05
647	IND Safety Reports (July 1-15, 2005)	7/18/05	N/A	N/A	N/A
648	Information Amendment:CMC Updated CMC information by cross-reference to NDA 21814 for drug substance and drug product documentation	7/18/05	NDA 21814	Cross reference NDA for drug substance and drug product documentation	To date.
7 day fax	7 day facsimile IND Safety Report 2005-BP-11727AU(0)	7/20/05	7/20/05	N/A	N/A
7 day fax	7 day facsimile IND safety report: 2005-FF00464FF(0)	7/21/05	N/A	N/A	N/A

EXHIBIT G

ELIGIBILITY OF PATENT FOR EXTENSION

ELIGIBILITY OF U.S. PATENT 5,852,195 FOR EXTENSION

In the opinion of the Applicant, U.S. Patent 5,852,195 is eligible for extension under the provisions of 35 U.S.C. §156, for the reasons which follow.

(1) The term of this patent has not expired before the submission of this application.

(2) The term of this patent has never been extended.

(3) This application for patent term extension is submitted by a registered practitioner on behalf of the record owner of the subject patent, Pharmacia & Upjohn LLC, by virtue of a power of appointment signed by a corporate official submitted simultaneously herewith as Exhibit H.

(4) The product has been subject to a regulatory review period before commercial marketing or use, pursuant to the provisions of Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355).

(5) The permission for commercial marketing or use of the product after the regulatory review period is the first permission for commercial marketing or use of the product under the provisions of the Federal Food, Drug and Cosmetic Act.

Applicant believes that the subject patent is entitled to 1278 days of extension.

The claimed length of extension has been calculated in the manner set forth in 37 C.F.R. §1.775, as follows:

Initially, the length of the regulatory review period was determined as set forth in section (c). It is 3115 days, which is the sum of:

(1) 2931days, the number of days in the period beginning on 13 December 1996, the date the exemption under subsection (I) of section 505 of the Federal Food, Drug and Cosmetic Act for the approved product (IND 51979) became effective, and ending on 21 December 2004, the date the application was initially submitted for such product under section 505(b) of the Federal Food, Drug and Cosmetic Act; and

(2) 184days, the number of days in the period beginning on 21 December 2004, the date the application (NDA 21-814) was initially submitted for the approved product under section 505 and ending on 22 June 2005, the date such application was approved.

Next, the term of the patent as extended was determined in accordance with subsection (d), by:

(1) subtracting from 3115 days, the number of days calculated above to be in the regulatory review period, 1835 days, which is the sum of the periods set forth in 37 C.F.R. §1.775 (d)(1)(i), (ii) and (iii) as set forth in the table below,

(i) the number of days in the periods of paragraphs (c)(1) and (c))(2) of 37 C.F.R. §1.775 which were on and before the date on which the patent issued	740 days
(ii) the number of days in the periods of paragraphs (c)(1) and (c)(2) of 37 C.F.R. §1.775 during which it is believed it will be determined , under 35 U.S.C. §156(d)(2)(B) by the Secretary of Health and Human Services that the Applicant did not act with due diligence	0 days
(iii) one-half of the number of days remaining in the period defined by paragraph (c)(1) of 37 C.F.R. §1.775 after that period is reduced in accordance with paragraphs (d)(1)(i) and (d)(1)(ii) of 37 C.F.R. §1.775 (ignoring half days for the purposes of subtraction)	1095 days

which calculation yields 1280 days as its result;

(2) by adding the number of days determined in accordance with 37 C.F.R. §1.775 (d)(1), which is 1280 days, to the original term of the patent as shortened by any terminal disclaimer (which term will expire on 22 December 2015), which calculation yields 24 June 2019 as its result;

(3) by adding 14 years to 22 June 2005, the date of approval of the application under section 505 of the Federal Food, Drug and Cosmetic Act, which calculation yields 22 June 2019 as its result;

(4) by comparing 24 June 2019 and 22 June 2019, the dates for the ends of the periods obtained pursuant to 37 C.F.R. §1.775 (d)(2) and (d)(3) with each other and selecting

the earlier date, which comparison yields 22 June 2019 as its result;

(5) as the original patent was issued after September 24, 1984,

(i) by adding five years to 22 December 2015, the original expiration date of the patent or any earlier date set by terminal disclaimer, which calculation yields 22 December 2020; and

(ii) by comparing 22 December 2020 and 22 June 2019, the dates obtained pursuant to 37 C.F.R. §1.775 (d)(4) and (d)(5)(i) with each other and selecting the earlier date, which comparison yields 22 June 2019 as its result.

The number of days between 22 December 2015, the original expiration date of the patent, and 22 June 2019, the approval date plus 14 years, is 1278 days, which is the amount of extension claimed.

EXHIBIT H

POWER APPOINTING REGISTERED PRACTITIONER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	: U.S. Patent 5,852,195
Issued	: December 22, 1998
Inventors	: Romines et al.
For	: PYRANONE COMPOUNDS USEFUL TO TREAT RETROVIRAL INFECTIONS

Mail Stop Patent Ext.
Director
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

APPOINTMENT OF AGENT

FOR PURPOSE OF

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Pharmacia & Upjohn Company LLC, a company organized under the laws of Delaware is the assignee and owner of record of U.S. Patent 5,852,195 by virtue of an assignment from each of the individual inventors which was recorded on November 23, 1998 at Reel/Frame 009609/0355.

Pharmacia & Upjohn Company LLC hereby appoints Alan Stempel, Reg. No. 28,991, Thomas Blankinship, Reg. No. 39,909, Anthony P. Bottino, Reg. No. 41,629, Philip I. Datlow, Reg. No. 41,482, Mary-Ellen M. Devlin, Reg. No. 27,928, David A. Dow, Reg. No. 46,124, Michael P. Morris, Reg. No. 34,513, Andrea Small, Reg. No. 54,859 and Timothy X. Witkowski, Reg. No. 40,232, as their attorneys and agents to represent Pharmacia & Upjohn LLC in all matters before the United States Patent and Trademark Office which relate to the filing or prosecution of an application for extension of the term of U.S. Patent 5,852,195 under 35 U.S.C.§ 156.

Respectfully submitted,

Steve T. Zelson
Assistant Secretary

US 088092240FP1

Creation date: 09-09-2005
Indexing Officer: TLAM2 - THY LAM
Team: OIPEBackFileIndexing
Dossier: 08809224

Legal Date: 09-02-2005

No.	Doccode	Number of pages
1	TERM.PTO.LET	1

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