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OBLON
SPIVAK
MCCLELLAND
MAIER
&
NEUSTADT
P.C.

ATTORNEYS AT LAW

STEPHEN G. BAXTER
(703) 413-3000
SBAXTER@OBLON.COM

MAIL STOP PATENT EXT.

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

RE: Serial No.: 08/809,723
Patentees: Hidenori OHKI et al
PCT Filed: September 29, 1995
For: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY
Group Art Unit: 1654
Examiner: Davenport, A. M.
Patent No.: 6,107,458
Issued: August 22, 2000

SIR:

Attached hereto for filing are the following papers:

APPLICATION FOR EXTENSION OF PATENT TERM WITH EXHIBITS A-G (FOUR COPIES)

Our credit card payment form in the amount of $1,120.00 is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. §1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Registration No. 32,884

Customer Number
22850
(703) 413-3000 (phone)
(703) 413-2220 (fax)

NDA-21

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DOCKET NO: 272499US0 SD

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE PATENT OF	:
HIDENORI OHKI ET AL	: GROUP ART UNIT: 1654
SERIAL NO: 08/809,723	: EXAMINER: DAVENPORT, A. M.
PCT FILED: SEPTEMBER 29, 1995	: PATENT NO. 6,107,458
FOR: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY	: ISSUED: AUGUST 22, 2000

APPLICATION FOR EXTENSION OF PATENT TERM UNDER

35 U.S.C. § 156 AND 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, 1.775 AND 1.785 (b)

MAIL STOP: PATENT TERM EXTENSION

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

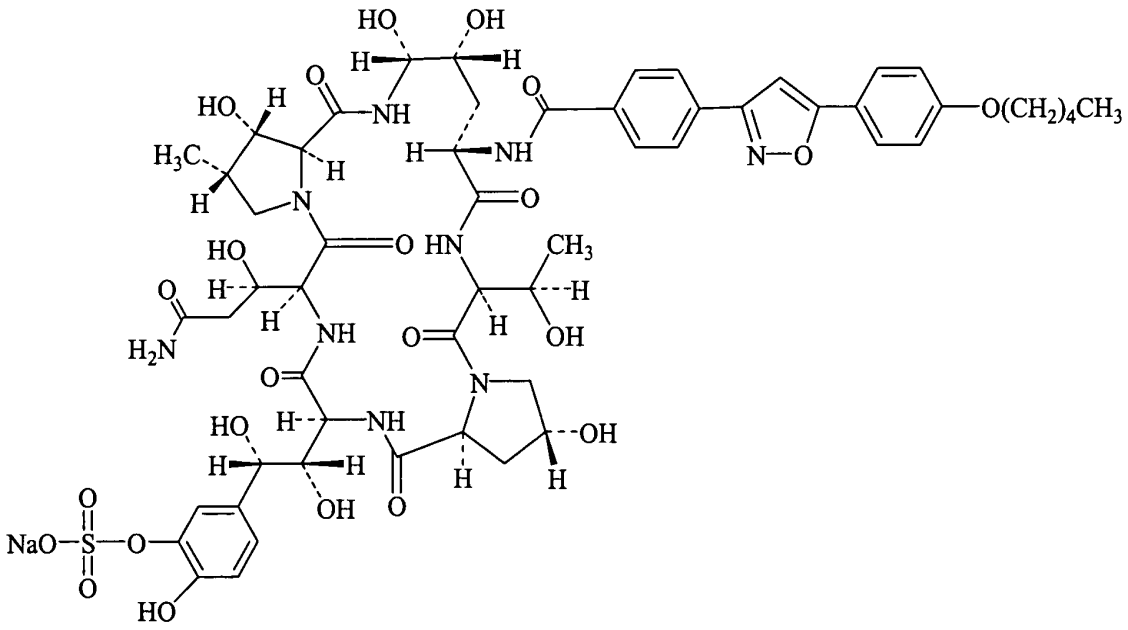
This is an application for extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, 1.775 and 1.785 (b) for U.S. Patent No. 6,107,458 ("the '458 patent"), based on NDA 21-754.

Three additional copies of this application are being submitted herewith (37 C.F.R. § 1.740(b)).

06/23/2005 TDEY11 00000001 6107458
01 FC:1457 1120.00 OP

I. Complete Identification of the Product (37 C.F.R. § 1.740(a)(1)).

The approved product is Mycamine, which is the registered name for injectable doses of lyophilized micafungin sodium. Each injectable dose contains 50 mg of the active ingredient: micafungin sodium. The chemical name for micafungin sodium is sodium 5-[(1S,2S)-2-[(3S,6S,9S,11R,15S,18S,20R,21R,24S,25S,26S)-3-[(R)-2-carbamoyl-1-hydroxyethyl]-11,20,21,25-tetrahydroxy-15-[(R)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-18-[4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoylamino]-1,4,7,13,16,22-hexaazatricyclo[22.3.0.$0^{9,13}$]heptacos-6-yl]-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate. The CAS Number is 179165-70-9. The molecular weight is 1292.27. The molecular formula is $C_{56}H_{70}N_9NaO_{23}S$, and it has the following structure:



Each dose of Mycamine contains 50 mg of micafungin sodium, 200 mg lactose, with citric acid and/or sodium hydroxide (used for pH adjustment).

II. Complete Identification of the Federal Statute Under which Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2)).

Regulatory permission to sell Mycamine was granted under 21 U.S.C. § 355 (section 505 of the Federal Food, Drug, and Cosmetic Act).

III. Identification of the Date on which the Product Received Approval (37 C.F.R. § 1.740(a)(3)).

Regulatory approval for Mycamine, based on NDA 21-754, was granted on March 16, 2005, and copy of the approval letter is attached hereto as Exhibit A.

IV. Identification of Each Active Ingredient and Statement that Each Active Ingredient has not been Previously Approved (37 C.F.R. § 1.740(a)(4)).

The sole active ingredient in the approved product is micafungin sodium. Micafungin sodium 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.

V. Statement that Application is being Submitted within the Sixty Day Period (37 C.F.R. § 1.740(a)(5)).

This application is being submitted within the sixty day period specified by 35 U.S.C. § 156(1) and 37 C.F.R. § 1.720(f).

VI. Complete Identification of the Patent (37 C.F.R. § 1.740(a)(6)).

The patent for which extension of patent term is sought is U.S. Patent No. 6,107,458 ("the '458 patent"), which names Hidenori Ohki, Masaki Tomishima, Akira Yamada, and Hisashi Takasugi as inventors, and which issued on August 22, 2000, from U.S. Patent Application Serial No. 08/809,723, and is currently set to expire on September 29, 2015.

VII. A Copy of the Patent for which Extension of Term is being Sought (37 C.F.R. § 1.740(a)(7)).

A copy of the '458 patent is attached hereto as Exhibit B.

VIII. Copies of any Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments, or Reexamination Certificates Issued in the Patent (37 C.F.R. § 1.740(a)(8)).

Applicants state on the record that no disclaimers have been filed in the '458 patent and that no reexamination certificate has been issued in the '458 patent.

A certificate of correction was issued on May 29, 2001, to correct the priority data. A copy of the May 29, 2001, certificate of correction is attached hereto as Exhibit C.

In addition, a request for a certificate of correction was filed on May 10, 2005, to correct a typographical error in the structure of formula (I) in claims 1 and 3 and a typographical error in the structure of formula (II) in claim 3. A copy of the request for a certificate of correction is attached hereto as Exhibit D.

A copy of the receipt of maintenance fee payment for the first maintenance fee in the '458 patent is attached hereto as Exhibit E.

IX. Statement that the Patent Claims the Approved Product (37 C.F.R. § 1.740(a)(9)).

The approved product, Mycamine, injectable micafungin sodium, is claimed in the '458 patent.

The following chart sets forth the relationship between the claims of the '458 patent and the approved product.

Claim of the '458 Patent	Mycamine
1. A polypeptide compound of the following general formula (I): [structure omitted] wherein R^1 is benzoyl substituted with isoxazolyl which has phenyl having lower alkoxy, or a salt thereof.	Mycamine contains micafungin sodium, which is the sodium salt of the compound of formula (I), when R^1 has the structure specified in claim 2, *i.e.*, when R^1 is a 4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoyl group.
2. A compound of claim 1, wherein R^1 is [structure omitted].	Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 2.
4. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1, or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or excipient.	Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 1, when R^1 has the structure specified in claim 2, *i.e.*, when R^1 is a 4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoyl group.
5. A method for the therapeutic treatment of infectious diseases caused by pathogenic microorganisms, comprising administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, to a human being or animal.	Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 1, when R^1 has the structure specified in claim 2, *i.e.*, when R^1 is a 4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoyl group.

It is noted that as printed, the structure for formula (I) in claims 1 and 3 contains a typographical error and that a request for certificate of correction has been filed to correct that typographical error. A detailed explanation of the typographical error and how it arose is provided in the request for certificate of correction, a copy of which is attached hereto as Exhibit D.

X. Statement of Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g) for a human drug (37 C.F.R. § 1.740(a)(10)(i)).

(A) The Effective Date of the IND and the IND number (37 C.F.R. § 1.740(a)(10)(i)(A)).

The effective date for the IND for the approved product is February 26, 1998, and the IND number for the approved product is IND 55,322. However, the amended protocol, protocol 03-7-005, which is the basis for NDA 21-754, was not filed in IND 55,322 until June 30, 2003. Thus, for the purposes of this application, the regulatory review period did not begin until June 30, 2003.

(B) The Date on which the NDA was Initially Submitted and the NDA Number (37 C.F.R. § 1.740(a)(10)(B)).

The NDA for the approved product was initially submitted on April 23, 2004, and the NDA number for the approved product is 21-754.

(C) The Date on which the NDA was Approved (37 C.F.R. § 1.740(a)(10)(C)).

NDA 21-754 was approved on March 16, 2005.

XI. Brief Description of Significant Activity Undertaken by the Marketing Applicant During the Applicable Regulatory Review Period and the Significant Dates Applicable to Such Activities (37 C.F.R. § 1.740(11)).

A. The IND.

A list of significant activities undertaken by the marketing applicant during IND 55,322 and the significant dates applicable thereto is provided in Table 1 below.

The following abbreviations are used in Table 1:

ANR	Annual Report
BD	Briefing Document (white paper)
CLIN	Clinical Information Amendment
CMC	CMC Information Amendment
GC	General Correspondence (e.g. Cross Reference Letters, Briefing Documents)
PHAS4	Phase 4 Commitment Response
PRO	Protocol (e.g. draft, new, new and revised investigators, revised, amendment)
PT	Pharmacology and Toxicology Information Amendment
SAE	Safety Report (Initial and Follow-up)

Table 1.

DATE	TYPE	DESCRIPTION
3/28/05	GC	Transfer Letter
3/24/05	SAE	IND Safety Reports – Initial and Follow-up
3/15/05	SAE	IND Safety Report – Follow-up
3/2/05	SAE	IND Safety Report – Follow-up
3/1/05	PRO	Protocol Amendment: Revised Protocol 03-0-192 incorporating Amendment 4
2/17/05	SAE	IND Safety Reports – Initial and Follow-up
2/14/05	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192
1/26/05	SAE	IND Safety Reports – Initial and Followup
1/12/05	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192
12/22/04	SAE	IND Safety Report – Initial and Followup
12/7/04	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192 and Revised Transfer of Obligations for -192
10/27/04	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192 and FG-463-21-08
10/20/04	SAE	IND Safety Report - Followup
10/5/01	SAE	IND Safety Report - Initial
10/1/04	CMC	Info Amendment: CMC – notified FDA to cross reference NDA 21-506 and 21-754 for updated CMC information for FK463 drug product
9/30/04	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192, Transfer of Obligations for -192
9/29/04	GC/PRO	Response to comments from FDA during 7/27/04 T-Con re: proposed closed testing procedure for study 03-0-192.
9/29/04	SAE	IND Safety Reports – F/U
9/17/04	SAE	IND Safety Report – Initial and F/U
9/9/04	SAE	IND Safety Report – Initial and F/U
9/1/04	PRO	Protocol Amendment: New Protocol 03-0-192, Amendments 1-3, Revised Protocol and Investigator Data (Sioson).
8/27/04	SAE	IND Safety Report – Initial

8/20/04	SAE	IND Safety Report – F/U
8/10/04	SAE	IND Safety Report – Initial and F/U
7/29/04	SAE	IND Safety Report – Initial
7/22/04	SAE	IND Safety Report – F/U
7/21/04	PRO	Protocol Amendment: Revised 1572s for Protocols 01-0-124 and FG-463-21-08
7/15/04	SAE	IND Safety Report – Initial and F/U
7/6/04	SAE	IND Safety Report – F/U
7/2/04	PRO	Response to FDA Response re: SPA for Protocol 03-0-192 (Amendment #2 and Revised Protocol)
6/23/04	SAE	IND Safety Report - Initial
6/10/04	ANR	Annual Report for reporting interval 11/27/02 – 11/26/03
6/3/04	SAE	IND Safety Report – F/U
5/28/04	PRO	Protocol Amendment: Revised 1572 for Protocol FG-463-21-08
5/26/04	SAE	IND Safety Report – Initial & F/U
5/24/04	PRO	Request for SPA – Clinical Protocol No. 04-0-199 (BAMSG #2-02) – included list of questions
5/11/04	SAE	IND Safety Report – Initial
4/29/04	SAE	IND Safety Report – Initial & F/U
4/28/04	PRO	Protocol Amendment: New Investigators for Protocol 03-7-005, Revised 1572s for Protocol FG-463-21-08 and 01-0-124
4/14/04	SAE	IND Safety Report – Initial & F/U
4/9/04	PRO	Special Protocol Assessment – Protocol 03-0-192 incorporating Amendment #1
4/8/04	SAE	IND Safety Report – Initial & F/U
4/7/04	SAE	IND Safety Report – F/U
4/7/04	PRO	Protocol Amendment: New Protocol 04-0-193, Admin Change #1, Transfer of Obligations, PI/CV for S. Reilley
3/30/04	SAE	IND Safety Report – Initial and F/U
3/18/04	SAE	IND Safety Report – Initial and F/U
3/16/04	PRO	Protocol Amendment: New Investigators for Protocol 03-7-005 and Revised 1572 for Protocol FG-463-21-08

3/10/04	SAE	IND Safety Report – Initial and F/U
2/19/04	SAE	IND Safety Report – F/U
2/5/04	PRO	Protocol Amendment: New Investigator for Protocol FG-463-21-08
1/30/04	SAE	IND Safety Report – F/U
1/20/04	SAE	IND Safety Report – F/U
1/9/04	PRO	Protocol Amendment: New Investigator for Protocol 98-0-047, Revised 1572s for FG-463-21-08, 01-0-124
1/8/04	SAE	IND Safety Report - Initial
12/23/03	SAE	IND Safety Report – Initial and Followup
12/10/03	SAE	Safety Report: Follow-up
12/5/03	PRO	Protocol Amendment: New Investigators for FG-463-21-08 and Revised Forms for same and 01-0-124
12/3/03	SAE	Safety Report: Initial
11/20/03	SAE	Safety Report: Follow-up
11/20/03	SAE	Safety Report: Initial
11/18/03	SAE	Safety Report: Follow-up
11/12/03	PRO	Submission of Micafungin Candidiasis Clinical Protocols (request of the FDA). 98-0-047, 03-7-005, FG-463-21-08, FG-463-21-09.
11/12/03	GC	Request for Pre-NDA Meeting
11/06/03	SAE	IND Safety Report: Initial
11/06/03	PRO	Protocol Amendment: New Investigators and Revised Forms 1572
11/04/03	SAE	IND Safety Report: Initial
10/30/03	SAE	IND Safety Report: Initial
10/28/03	SAE	IND Safety Report - Followup
10/24/03	BD	Briefing Document for New EC NDA (meeting to be held November 24, 2003)
10/23/03	SAE	IND Safety Report - Followup
10/22/03	CLIN	Addendum to Edition 4 of the IB
10/14/03	SAE	IND Safety Report - Initial

10/14/03	SAE	IND Safety Report - Followup
10/14/03	SAE	IND Safety Report - Initial
10/10/03	PRO	Protocol Amendment: Change in protocol 03-7-005 and draft IAP
9/30/03	SAE	IND Safety Report - Initial
9/29/03	PRO	Protocol Amendment: New Investigators and Revised 1572s
9/26/03	SAE	IND Safety Report - Followup
9/26/03	SAE	IND Safety Report - Followup
9/23/03	SAE	IND Safety Report - Initial
9/16/03	SAE	IND Safety Report - Followup
9/12/03	SAE	IND Safety Report - Followup
9/10/03	SAE	IND Safety Report - Initial
9/9/03	SAE	IND Safety Report - Followups
9/9/03	PRO	Protocol Amendment: New Protocols (03-0-175, 03-0-176, 03-0-177, 03-0-178), Admin Change 01 to all 4 protocols, Investigator Information.
9/5/03	SAE	IND Safety Report - Followup
9/3/03	SAE	IND Safety Report - Followup
08/29/03	PRO	Protocol Amendment: New Protocol (FG-463-21-08) and Investigator Information (McNeil)
08/28/03	SAE	IND Safety Report - Initial
08/27/03	SAE	IND Safety Report - Followup
08/21/03	SAE	IND Safety Report - Initial
08/20/03	SAE	IND Safety Report - Followup
08/14/03	SAE	IND Safety Report - Initial
08/12/03	SAE	IND Safety Report - Initial
08/08/03	SAE	IND Safety Report – Initial and Followup
08/07/03	SAE	IND Safety Report - Initial
08/01/03	SAE	IND Safety Report - Initial

07/30/03	SAE	IND Safety Report - Initial
07/24/03	SAE	IND Safety Report - Initial
07/18/03	SAE	IND Safety Report - Followup
07/09/03	SAE	IND Safety Reports: Initial and Followup.
07/03/03	GC	Proposal for New NDA Esophageal Candidiasis (Fujisawa's Proposal to Address Issues Raised in the Division's May 23, 2003 Letter concerning the Minimum 300 subjects receiving FK463 at a dose of 150 mg/day for 10 days).
06/30/03	PRO	Protocol Amendment: New Protocol 03-7-005
06/27/03	SAE	IND Safety Reports - Initial
06/25/03	PRO	Protocol Amendment: New Investigators for Protocol 01-0-124 and Revised Forms FDA 1572 for Protocols 98-0-046 and 01-0-124
6/17/03	SAE	IND Safety Reports - Initial
6/10/03	SAE	IND Safety Reports – Initial and Followup
6/3/03	SAE	IND Safety Reports - Followups
5/21/03	SAE	IND Safety Reports - Followups
5/16/03	PRO	Protocol Amendment: New Investigators and Revised Form FDA 1572 for 046, 124
5/6/03	SAE	IND Safety Reports – Initial
5/5/03	ANR	Annual Report 11/27/01-11/26/02
4/29/03	SAE	IND Safety Reports – Initial and Followup
4/18/03	SAE	IND Safety Reports – Initial and Followup
4/9/03	PRO	Protocol Amendment: New Investigators and Revised Form FDA 1572 for 046, 124, and 125
4/4/03	SAE	IND Safety Reports - Followup
3/26/03	PRO	Protocol Amendment: Amendment 02 to Protocol 01-0-124
3/21/03	SAE	IND Safety Report - Initial
3/14/03	SAE	IND Safety Reports -Followup
3/13/03	SAE	IND Safety Reports-Followup (FAX) Same as Serial 158 Hard-copy)
3/7/03	PRO	Protocol Amendment: New Investigators for 01-0-124

2/27/03	SAE	IND Safety Reports– Initial and Followup
2/18/03	SAE	IND Safety Reports- Initial
2/17/03	PRO	Protocol Amendment: New Investigators and Revised 1572 for 01-0-124
1/3/03	PRO	Protocol Amendment: New Investigator for 01-0-124 & revised 1572 for 98-0-047
12/13/02	PRO	Protocol Amendment: Revised Transfer of Obligations for -124 and -125
12/10/02	SAE	IND Safety Report - Followup
11/25/02	PRO	Protocol Amendment: Revised 1572s for 98-0-046 & 98-0-047
11/5/02	PRO	Protocol Amendment: New Protocol 01-0-125 & Investigator Information for N. Seibel
10/23/02	PRO	Protocol Amendment 1 to Protocol 01-0-124 and Investigator Information
10/3/02	PRO	Protocol Amendment: New Investigators for 98-0-046, 98-0-047 & 99-0-063; Revised 1572s for 98-0-046 & 98-0-047
9/27/02	ANR	Annual Report 11/27/00-11/26/01
9/26/02	SAE	IND Safety Report (15-day)
08/30/02	PRO	Protocol Amendment: Revised 1572s for 98-0-046 & 98-0-047
08/9/02	SAE	IND Safety Report (15-day)
07/31/02	PRO	Pre-emptive White Paper/Protocol 01-0-124 (received acknowledgement letter from FDA dated 10/8/02)
07/26/02	SAE	Follow-up IND Safety Report (15-day)
07/18/02	PRO	Protocol Amendment: Revised 1572s for 98-0-046, 98-0-047, and 99-0-063
06/14/02	SAE	Initial IND Safety Report (15 day)
5/10/02	PRO	Protocol Amendment – Revised 1572s for 98-0-046, 98-0-047, and 98-0-050
4/8/02	GEN	General Correspondence: Response to FDA's Fax dated 4/3/02 re: FHI's submission of proposed SAS datasets and data def files (Serial No. 132)
04/03/02	SAE	Follow-up IND Safety Report (15-day)
03/15/02	PRO	Protocol Amendment – New Investigator (Myint) for 98-0-046; Revised 1572s for 98-0-046, 98-0-047, and 99-0-063
03/13/02	SAE	Initial IND Safety Report (15-day)
03/08/02	GEN	Submission of Proposed Archival SAS datasets and data definition files (–050 Study) and proposed SAS datasets (SHAM) for Reviwer Aids

02/28/02	SAE	Follow-up IND Safety Report (15-day)
02/15/02	PRO	Protocol Amendment – New Investigators/CVs and Revised 1572s for 98-0-046, 98-0-047, 98-0-050. Revised 1572s for 01-0-110 and 01-0-111.
02/12/02	SAE	Initial IND Safety Report (15-day)
01/16/02	PRO	Protocol Amendment – New Investigators and Revised 1572s for 98-0-046, 98-0-047
11/09/01	PRO	Protocol Amendment – New Investigators for 98-0-046, 98-0-047, 01-0-110, 01-0-111
11/8/01	GC	Request for Meeting with Stat and Medical Reviewers to discuss proposed SAS datasets and proposed format of data definition files (submitted on CD-ROM)
10/26/01	GC	Summary of micafungin dosing
10/12/01	PRO	Protocol Amendment: New Investigators to 98-0-046 98-0-057, 98-0-050 , 99-0-063 and revised 1572s
9/20/01	PRO	Protocol Amendment: New Protocols (01-0-105, 110, 111) and 1572/CV Information for each protocol
8/29/01	PRO	Protocol Amendment: New Protocol (01-0-104) and 1572/CV for S. Austin
8/28/01	SAE	Follow-up IND Safety Report (15-day)
8/3/01	SAE	Initial IND Safety Report (15-day)
7/13/01	SAE	Initial IND Safety Report (15-day)
7/5/01	GEN	Submission of e-mail correspondence between R. Reed (FHI) and L. Chan (FDA). Communications dated 6/29/01 and 7/03/01
6/29/01	GEN	Submission of 4 Draft Protocol Synopses
6/14/01	PRO/IB	Submission of Revised IB and Amendment 2 to Protocol 99-0-063
6/13/01	SAE	IND F/U Safety Report
6/1/01	PRO	Protocol Amendment-New Investigators and Revised 1572s
5/29/01	SAE	IND Safety Alert Report
5/18/01	SAE	IND Safety Alert Report
4/19/01	BRFDOC	Submission of Pre-NDA Briefing Document
4/6/01	GC	Request for a teleconference
4/3/01	PRO	Protocol Amendment: New and revised 1572s
4/3/01	ANR	Annual Report
2/20/01	PRO	Protocol Amendment: New and revised 1572s

12/27/00	PRO	Protocol Amendment: New and revised 1572s
12/12/00	SAE	15-day Alert Report
11/16/00	PRO	New protocol (99-0-063) and investigator to it.
11/15/00	SAE	15-day Alert Report
11/6/00	PRO	Protocol Amendment: new and revised 1572s
10/27/00	SAE	15-day Alert Report
9/21/00	PRO	Protocol amendment: new and revised 1572s.
8/22/00	SAE	15-day Alert Report
8/4/00	SAE	15-day Alert Report
7/31/00	PRO	Protocol Amendment: New and revised 1572s.
7/7/00	PRO	Protocol Amendment: New Investigators
6/9/00	SAE	15-day Alert Report
6/6/00	AMEND	Information Amendment: Clinical pK study for 98-0-040
5/30/00	PRO	Protocol Amendment: New Investigators
5/9/00	SAE	15-day Alert Report
5/5/00	PRO	Protocol Amendment: New Investigators and revised information to 98-0-046, 98-0-047, and 98-0-050
5/3/00	PRO	Protocol Amendments: Change in protocol 98-0-046 and 98-0-047 (Amendments 4)
04/12/00	PRO	Protocol Amendment: New Investigators and revised 1572s to 98-0-050, 98-0-046 and 98-0-047
03/22/00	PRO	Protocol Amendment: New Investigators
03/07/00	AMEND	Amendment to Annual Report; submitted two stability reports RAR000097 and RAR000098
03/01/00	SAE	15-day Alert Report
03/01/00	ANR	Annual Report 11/27/98 to 11/26/99
02/28/00	PRO	Protocol Amendment: New Investigators to 98-0-050, 98-0-046 and 98-0-047
02/25/00	SAE	15-day Alert Report
02/15/00	PRO	Protocol Amendment: New Investigators to 98-0-050 and revised 1572s
02/11/00	SAE	15-day Alert Report

02/10/00	SAE	15 day alert report
02/02/00	SAE	Follow-up safety report
01/26/00	AMEND	Information Amendment: Clinical pK study L1999000044 for Protocol 97-0-041
01/20/00	SAE	Initial safety report
01/19/00	PRO	Protocol Amendment: New Investigators to 98-0-050
01/05/00	PAE	15-day Alert report
12/20/99	PRO	Protocol Amendment: New investigators to 98-0-050
12/15/99	AMEND	CMC Amendment to the drug product
12/9/99	SAE	IND Safety report submitted to FDA for one initial report
12/9/99	PRO	Protocol Amendment: New Investigators to 98-0-046, 98-0-047 and 98-0-050
12/8/99	AMEND	Information Amendment: Clinical. Final report for Protocol 97-0-041 entitled "A phase I/II study to determine the maximum tolerated dose and pharmacokinetics of FK463 in combination with fluconazole for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant."
12/3/99	SAE	15-day Follow-up Safety Report
11/30/99	LTR	General Correspondence : Request to FDA to review Drug Master File
11/10/99	PRO	Protocol Amendment: New investigators to 98-0-046 and 98-0-047
11/04/99	SAE	Two IND initial safety reports submitted to FDA
11/03/99	PRO	Protocol Amendment: Change in Protocol 98-0-043: to increase dose to be evaluated to include 3.0 and 4.0 mg/kg/day and administrative changes
10/28/99	PRO	Protocol Amendment: New Protocol (98-0-050), Amendment 01 and first investigator
10/26/99	LTR	Response to FDA EOP2 Meeting minutes from 9/10 meeting
10/22/99	SAE	1 initial report
10/19/99	PRO	Protocol Amendment: New Investigators to 97-0-047
10/05/99	SAE	IND Safety Report: 1 follow-up safety report submitted to FDA
09/14/99	PRO	Protocol Amendment: New Investigators to 98-0-043, 98-0-046 and 98-0-047
09/17/99	SAE	IND Safety Reports – 2 initial reports submitted to FDA
09/02/99	LTR	Additional Information for EOP2 Meeting: Revision to question

		#5
08/25/99	LTR	End of Phase 2 Meeting Agenda and List of Attendees for FHI
08/24/99	SAE	IND Safety Report – 1 follow up report
08/11/99	PRO	Protocol Amendment: New Investigators.
08/05/99	LTR	End of phase 2 Briefing Document
08/05/99	SAE	15 day /alert report
07/20/99	AMEND	Information Amendment: Pharm./Tox Report GLR980160
07/13/99	PRO	Protocol Amendment: New Investigators to: 98-0-046 and 98-0-47
07/01/99	PRO	Protocol Amendment: New Investigators New investigators to 98-0-046 and 98-0-047.
06/30/99	AMEND	Information Amendment: Pharm./Tox. Reports CRD980156, CRD980083, GLR980003, CRD980043 and GLR980004.
06/29/99	SAE	IND Safety Report – follow-up report submitted to FDA
06/23/99	SAE	IND Safety Reports – follow-up reports submitted to FDA
06/09/99	PRO	Protocol Amendment: Change in Protocol Change in protocol 98-0-042 (to increase dose to 2.0 mg/kg/day, the rationale for doing so and administrative changes.
06/09/99	PRO	Protocol Amendment: Change in Protocol Change in European protocols FG463-21-01 and FG463-21-02
06/09/99	PRO	Protocol Amendment: New Investigators New investigators added to Protocol 98-0-046 and 98-0-047
05/20/99	SAE	IND Safety Report
05/06/99	PRO	Protocol Amendment: New Investigators New investigators added to Protocol 98-0-046 and 98-0-047.
05/05/99	SAE	IND Safety Report – initial report submitted to FDA
04/30/99	PRO	Protocol Amendment: Change in Protocols Change in Protocol 98-0-046, increase initial dose to 75 mg/day, etc. To 98-0-047, dose adjustments to 150 mg/day, etc.
04/14/99	PRO	Protocol Amendment: New Investigators Protocol 98-0-046 and Protocol 98-0-047

04/02/99	PRO	Protocol Amendment: New Investigators New Investigators added to protocol 98-0-047
03/30/99	AMEND	Information Amendment: Pharmacology/ Toxicology: FK463 and an amendment to the final report, 4 week IV toxicity study of FR179463 in rats with recovery study (GLR970116); a copy of report GLR980020 re: Single dose IV toxicity study of photo-degradated FK463 product in rats.
03/26/99	LTR	Response to FDA fax dated 1/19/99 Response to the FDA fax of 1/1/9/99 re: 4 attachments, agency's comments and FHI responses, QC sample data for studies CLR980023 and CLR980025; report titled PK of FK463 in Phase I repeated dose study; survival data that support ED50 values in reports CRR980116 and CRR980117.
03/24/99	PRO	Protocol Amendment: Change in Protocol Letter sent to FDA on 3/24/99 re: Change in Protocols 98-0-046 and 98-0-047 for exclusion of de novo patients at Canadian sites.
03/23/99	PRO	Protocol Amendment: New Investigator 98-0-046 and 98-0-047 .
03/16/99	LTR	FHI Meeting Minutes Minutes of 2/5/99 teleconference with FDA
03/16/99	PRO	Protocol Amendment: New Investigator Protocol 98-0-046 and 98-0-047
03/15/99	ANR	Annual Report Reporting interval 03/26/98 to 11/26/98
03/11/99	PRO	Protocol Amendment: New Investigator Protocol 98-0-043
03/03/99	SAE	IND Safety Report One initial safety report submitted on 3/3/99
03/02/99	PRO	Protocol Amendment: New Investigators Protocols 98-0-046 and 98-0-047;
02/23/99	PRO	Protocol Amendment: New Protocols, Protocol Amendment and New Investigator Protocol 98-0-047 "An Open-Label, Non-comparative Study of FK463 in the Treatment of Candidemia or Invasive Candidiasis", Amendment 01 to adjust the initial dose, to update the reconstitution procedures and to include regulatory agencies in addition to FDA; Protocol FG463-21-02 (European of same name as 98-0-047); and new investigator
02/23/99	GC	Response to FDA Letter FHI response to 12/4/98 letter regarding Serial numbers 014 and 015

02/12/99	PRO	Protocol Amendment: Change in protocol Amendment #4 Increase dose to be evaluated to 200 mg (protocol 97-0-041)
02/03/99	PRO	Protocol Amendment: New Protocol, amendment and New Investigator: Protocols 98-0-046 (US) and FG463-21-01 (European) "An Open-Label Non-Comparative Study of FK463 for the Treatment of Invasive Aspergillosis:, Amendment 01 to 98-0-046 and New Investigator.
01/20/99	GC	General Correspondence End-of-Phase 2 Meeting Request for mid-April
01/07/99	PRO	Protocol Amendment: New Investigator Protocol 97-0-041, Dr. Pranatharthi Chandrasekar
12/28/98	PRO	Protocol Amendment: New DRAFT Protocol Protocol 98-0-050 "A Phase III Randomized Double Blind Comparative Trial of FK463 versus Fluconazole for Prophylaxis of Fungal Infections in Patients Undergoing Bone Marrow or Peripheral Stem Cell Transplantation
12/07/98	PRO	Protocol Amendment: New Investigator N. Chao to 97-0-041
11/20/98	PRO	Protocol Amendment: New Investigator P. Flynn to 98-0-043
11/19/98	AMEND	Information Amendment: CMC Labeling change to clinical trial labels
11/13/98	PRO	Protocol Amendment: New Investigator T. Walsh to Protocol 98-0-043
11/4/98	PRO	Protocol Amendment: Change in protocol Change to 97-0-041; Amendment 03 increase dose from 100 mg/day to 150 mg/day
10/28/98	PRO	Protocol Amendment: New Protocol 98-0-043, Amendment 01 to this protocol and new investigator (Nita Seibel).
10/26/98	SAE	IND Safety Report
10/8/98	PRO	Protocol Amendment: New Investigators S. Devine and D. Simpson to 97-0-041
10/6/98	AMEND	Information Amendment: Clinical 2 non-IND clinical trial reports CLR980023 (R98-0224-463-C1-E) Phase 1 Single-Dose Intravenous Administration Study of FK463; CLR980025 (R98-0223-463-C1-E) Phase 1 Repeated Dose Intravenous Administration Study of FK463.
10/6/98	AMEND	Information Amendment - Pharm/Tox Three Non-clinical Reports: CRR980115 (R98-0200-463-P1-E) Prophylactic effect of FK463 against Pneumocystis carinii infection in mice. CRR980116 (R98-0201-463-P1-E) Efficacy of intravenous injection of

		FK463 in mouse models of pulmonary candidiasis and aspergillosis. CRR980117 (R98-0202-463-P1-E) Efficacy of intravenous injection of FK463 in mouse models of disseminated candidiasis and aspergillosis
8/4/98	PRO	Protocol Amendment: Change in Protocol 97-0-041 Amendment 2: Enrollment of allogeneic bone marrow or peripheral stem cell transplant patients.
7/6/98	AMEND	Information Amendment Response to May 1 letter of request and recommendations
6/15/98	PRO	Protocol Amendment – New Investigator New 1572s to 97-0-041 P. Cagnoni and J. Hiemenz
6/8/98	PRO	Protocol Amendment Change in Protocol 97-0-040 and an addendum to the Informed Consent Form.
6/3/98	LTR	Change in Corporate Name to FHI
5/14/98	PRO	Protocol Amendment – New Investigator To protocol 97-0-040 J. Kisicki
5/15/98	AMEND	Information Amendment - Pharm./Tox. 6 reports for as pharmacological and metabolic support: CRD980078, CRD980079, CRD980084, GLR980047, GLR980049 and GLR980048
4/13/98	PRO	Protocol Amendment Submission of requested information - 14-C Study, Informed Consent and amount of radiation per patient. (4/21/98 - This was returned by FDA as it was sent to the Fishers Lane address via Fed. Ex. By direction of A. Chun. Fishers Lane does not accept Fed. Ex. Packages. Was resubmitted to the Division via Fed. Ex
4/1/98	PRO	Protocol Amendment Revised protocol 97-0-041 to clarify the collection and processing of blood samples for pharmacokinetics analysis
02/26/98	IND	Original IND

B. The NDA.

A list of significant activities undertaken by the marketing applicant during the review of NDA 21-754 and the significant dates applicable thereto is provided in Table 2 below.

The following abbreviations are used in Table 2:

AMEND	Amendment to NDA or sNDA
ANR	Annual Report
FIELD	District Office Copy of CMC Supplement
GC	General Correspondence (e.g. Cross Reference Letters, Briefing Documents)
PHAS4	Phase 4 Commitments
PSUR	Periodic Safety Update Report
SUPL	Supplement

Table 2.

DATE	TYPE	DESCRIPTION
4/15/05A	GC	Forms FDA 3542 – Patent Information for Mycamine desk copies sent to Christina Chi (faxed to division on 4/15/2005)
4/15/05	SUPL	Changes Being Effected – Supplement (CBE-30 Alternative-Closure Configuration)
4/4/05	GC	Acceptance Letter
3/31/05	GC/LABEL	Submission of FPL (FHI) as required in approval letter (submitted electronically to both NDA 21-506 and 21-754). This represents the last submission to NDA 21-754 – all future submissions will be submitted to NDA 21-506 only
	GC	Transfer Letter

DATE	TYPE	DESCRIPTION
3/10/05A	GC	Submission of proposed press release for review and comment (including current draft PI dated 3/7/05). Note document was also submitted to DDMAC for their review and comment as well.
3/10/05	AMEND	Submitted latest versions of draft labeling - PI dated 3/7/05 and Vial/Carton dated 3/10/05 as submitted via e-mail (Submitted electronically to both NDA 21-754 and 21-506)
3/9/05	AMEND	Submitted latest versions of draft labeling - PI dated 3/7/05 and Vial/Carton dated 2/24/05 as submitted via e-mail (Submitted electronically to both NDA 21-754 and 21-506)
3/8/05	AMEND	Response to 3/4/05 e-mail request – Prophylaxis Efficacy Results (Submitted electronically to both NDA 21-754 and 21-506)
2/22/05	AMEND	Response to FDA Request for Information dated 2/21/05 (item-by-item response to comments raised by Microbiologist in a 3/23/03 e-mail). Also included in submission were the draft carton and container labeling for Mycamine (50 mg strength), which incorporated comments from the Division during 2/18/05 discussion.
2/18/05	AMEND	Response to FDA Request for Information dated 2/17/05 regarding reevaluation of Serious Hepatic Adverse Events and Hepatic Laboratory Changes.
2/11/05	AMEND	Response to Info Request Dated 2/4/05 (Division re-defined request on 2/10) and Response to Item 2 in 2/7/05 e-mail request. Submitted electronically to both NDA 21-754 and 21-506.

DATE	TYPE	DESCRIPTION
2/4/05A	AMEND	Response to FDA E-Mail request dated 2/3/05 (info re: Study -050). Complete response with exception requested SAS dataset
2/4/05	AMEND	Response to FDA E-Mail request dated 2/2/05 (clinical). Also included patient narratives requested in 2/1/05 request. Submitted electronically to both NDA 21-754 and 21-506
2/3/05	AMEND	Submission of FDA Form 3542a (Patent Certification) for new patent for Mycamine and statement to FDA that Fujisawa does NOT wish to pursue commercialization of the 25 mg product formulation at this time. Submitted electronically to both NDA 21-754 and 21-506
2/2/05	AMEND	Response to FDA E-mail request dated 2/1/05 – Response submitted electronically to both NDA 21-754 and 21-506
1/27/05	AMEND	Response to FDA Request for Information Dated 1/26/05 (E-mail from Dr. Singer). Also included was final compatibility report requested on 1/14/05, official submission of Medwatch forms requested 1/24/05 and proposed vial/carton labeling requested 1/25/05
1/26/05	AMEND	Final Response to FDA Info Request Dated 12/14/04 (Clinical) – completes the response to this request (submitted to both NDA 21-754 and 21-506)
1/10/05B	AMEND	Response to FDA Request for Information Dated 1/6/05 from Biostats Reviewer – Datasets submitted in SAS format (as requested) to NDA 21-754
1/10/05A	AMEND	Response to FDA Request for Information Dated 1/5/05 from Clinical Reviewer – Response submitted in full (electronically) to both NDA 21-754 and 21-506
1/10/05	AMEND	Response to FDA Request for Information Dated 1/3/05 from Clinical Reviewer – Response submitted in full (electronically) to both NDA 21-754 and 21-506
1/6/05	AMEND	Response to FDA Request for Information dated 12/22/05 from Clinical Reviewer (additional safety information and datasets for patients across several studies). Sent to both NDA 21-506 and 21-754
12/23/04	AMEND	Partial response to FDA Request for Information Dated 12/21/04 (Fax from Clinical Reviewer) – response submitted in full (electronically) to both NDA 21-506 and 21-754 (submission of requested datasets were NOT included)
12/22/04	AMEND	Response to FDA Request for Information Dated 12/14/04 (Fax from Clinical Reviewer) – response submitted in full (electronically) to both NDA 21-506 and 21-754. It was noted that several items would be submitted under separate cover when available.
12/1/04	AMEND	Response to FDA Request for Information Dated 10/27/04 from Clinical Reviewer (Item #2 – Expert Hematologist

DATE	TYPE	DESCRIPTION
		Panel Review)
11/18/04	AMEND	Response to FDA Request for Information Dated 11/15/04 from Clinical Reviewer
11/12/04	AMEND	Response to FDA Request for Information Dated 10/27/04 from Clinical Reviewer (except for Item #2)
10/20/04	AMEND	Response to FDA Request for Information Dated 10/19/04 from Chemistry & Microbiology Reviewers
10/1/04	GC	Submitted copy of IND Serial submission (Serial No. 262) submitted to provide for cross reference information to NDAs 21-506 and 21-754 for drug product
9/22/04	AMEND	Response to FDA's September 10, 2004 Request for Additional Clinical Information (full response).
8/24/04	AMEND	Submission of Section 9: 120-day Safety Update and Updated Labeling (package insert) – FSR for 03-7-005 and FG14 were also included
5/11/04	AMEND	Updated Patent Certification/Information on Forms 3542a (3 patents were submitted) submitted to NDA
4/23/04	ORIGINAL	Submission of Original NDA (electronic DLT Tape submitted to FDA) – no hard copies provided

XII. Statement that in the Opinion of the Applicant the Patent is Eligible for Extension of Patent Term and Statement as to the Length of extension and how the Length was Determined (37 C.F.R. § 1.740(a)(12)).

In the opinion of the applicant, the '458 patent is eligible for extension. In the opinion of the applicant, the '458 patent is entitled to be extended 476 days, *i.e.*, the '458 patent is entitled to an extended expiration date of January 17, 2017. The extension of 476 days was calculated by the method described in 37 C.F.R. § 1.775.

The number of days by which the '458 patent should be extended was calculated as follows:

A. The minimum number of days in the regulatory review period was calculated according to 37 C.F.R. § 1.775(c) and reduced as appropriate pursuant to 37 C.F.R. §§ 1.775(d)(1)-(6).

B. The minimum number of days in the regulatory review was calculated by adding the number of days pursuant to (37 C.F.R. § 1.775(c)(1)) and the minimum number of days pursuant to (37 C.F.R. § 1.775(c)(2)).

C. The number of days pursuant to (37 C.F.R. § 1.775(c)(1)) was calculated as the number of days in the period from the date on which IND 55,322 was amended to include the protocol on which NDA 21-754 was based, June 30, 2003, and ending on the date NDA 21-754 was submitted, April 23, 2004, and determined to be 298 days.

D. The minimum number of days pursuant to (37 C.F.R. § 1.775(c)(2)) was calculated as the number of days in the period starting from the date NDA 21-754 was submitted, April 23, 2004, and ending on the date of approval of NDA 21-754, March 16, 2005, and determined to be 327 days.

E. Thus, the minimum number of days in the regulatory review was calculated by adding 298 days to 327 days and determined to be 625 days

F. The number of days to be subtracted from the regulatory review period under 37 C.F.R. § 1.775(d)(1) was calculated by determining the number of days pursuant to each of C.F.R. §§ 1.775(d)(1)(i)-(iii).

G. Since the regulatory review period began on June 30, 2003, and since the '458 patent issued on August 22, 2000, 0 days in the regulatory review period were on or before the date on which the '458 patent issued. Thus, the number of days pursuant to C.F.R. § 1.775(d)(1)(i) was determined to be 0.

H. As set forth above, applicants have acted with due diligence during the entire regulatory review period. Thus, the number of days pursuant to C.F.R. § 1.775(d)(1)(ii) was determined to be 0.

I. The number of days pursuant to C.F.R. § 1.775(d)(1)(iii) was calculated by dividing the number of days pursuant to 37 C.F.R. § 1.775(c)(1), 298 days, in half and determined to be 149 days.

J. The number of days pursuant to C.F.R. § 1.775(d)(1) was calculated by subtracting the number of days calculated pursuant to C.F.R. § 1.775(d)(1)(iii), 149 days, from the number of days calculated pursuant to C.F.R. § 1.775(c), 625 days, and determined to be 476 days.

K. The term of the '458 patent as extended as determined by C.F.R. § 1.775(d)(2) was calculated by adding the number of days calculated pursuant to C.F.R. § 1.775(d)(1), 476 days, to the original term of the '458 patent (current expiration date September 29, 2015) and determined to be January 17, 2017.

L. The term of the '458 patent as extended as determined by C.F.R. § 1.775(d)(3) was calculated by adding 14 years to the date of approval, March 16, 2005, and determined to be March 16, 2019.

M. The term of the '458 patent as extended as determined by C.F.R. § 1.775(d)(4) was calculated by comparing the dates calculated pursuant to C.F.R. § 1.775(d)(3) and C.F.R. § 1.775(d)(4) and selecting the earlier date and determined to be January 17, 2017.

N. The term of the '458 patent as extended as determined by C.F.R. § 1.775(d)(5)(i) was calculated by adding five years to the original expiration date of the '458 patent (September 29, 2015) and determined to be September 29, 2020.

O. The term of the '458 patent as extended as determined by C.F.R. § 1.775(d)(5)(ii) was calculated by selecting the earlier date pursuant to C.F.R. § 1.775(d)(4) and C.F.R. § 1.775(d)(5)(i) and determined to be January 17, 2017.

P. Since the '458 patent issued after September 24, 1984, no adjustment was made under C.F.R. § 1.775(d)(6).

XIII. Statement that Applicant Acknowledges a Duty to Disclose any Information which is Material to the Determination of the Entitlement to the Extension Sought (37 C.F.R. §§ 1.740(a)(13) and 1.765).

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 or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

It is understood that the duty of candor and good faith toward the Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture rests on the patent owner or its agent, on each attorney or agent who represents the patent owner and on every other individual who is substantively involved on behalf of the patent owner in a patent term extension proceeding. All such individuals who are aware, or become aware, of material information adverse to a determination of entitlement to the extension sought, which has not been previously made of record in the patent term extension proceeding must bring such information to the attention of the Office or the Secretary, as appropriate, as soon as it is practical to do so after the individual becomes aware of the information. Information is material where there is a substantial likelihood that the Office or the Secretary would consider it important in determinations to be made in the patent term extension proceeding. 37 C.F.R. § 1.765(a).

It is also understood that disclosures pursuant to this section must be accompanied by a copy of each written document which is being disclosed. The disclosure must be made to the Office or the Secretary, as appropriate, unless the disclosure is material to determinations to be made by both the Office and the Secretary, in which case duplicate copies, certified as such, must be filed in the Office and with the Secretary. Disclosures pursuant to this section may be made to the Office or the Secretary, as appropriate, through an attorney or agent having responsibility on behalf of the patent owner or its agent for the patent term extension

proceeding or through a patent owner acting on his or her own behalf. Disclosure to such an attorney, agent or patent owner shall satisfy the duty of any other individual. Such an attorney, agent or patent owner has no duty to transmit information which is not material to the determination of entitlement to the extension sought. 37 C.F.R. § 1.765(b).

It is further understood that no patent will be determined eligible for extension and no extension will be issued if it is determined that fraud on the Office or the Secretary was practiced or attempted or the duty of disclosure was violated through bad faith or gross negligence in connection with the patent term extension proceeding. If it is established by clear and convincing evidence that any fraud was practiced or attempted on the Office or the Secretary in connection with the patent term extension proceeding or that there was any violation of the duty of disclosure through bad faith or gross negligence in connection with the patent term extension proceeding, a final determination will be made that the patent is not eligible for extension. 37 C.F.R. § 1.765(c).

In compliance of the duty of disclosure, it is acknowledged that two additional applications for term extension for two additional patents based on the regulatory review of Mycamine are also being filed. Specifically:

1. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 was filed for U.S. Patent No. 6,107,458 (attorney docket no. 271987US0SD) on May 12, 2005;

2. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 is also being filed for U.S. Patent No. 5,376,634 (attorney docket no. 270677US0SD);

3. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 is also being filed for U.S. Patent No. 6,265,536 (attorney docket no. 271988US0SD);

4. An application for term extension based on the regulatory review of Mycamine under NDA 21-754 is also being filed for U.S. Patent No. 5,376,634 (attorney docket no. 272498US0SD); and

5. An application for term extension based on the regulatory review of Mycamine under NDA 21-754 is also being filed for U.S. Patent No. 6,265,536 (attorney docket no. 272500US0SD).

XIV. Prescribed Fee (37 C.F.R. § 1.740(a)(14)).

The fee as prescribed in 37 C.F.R. § 1.20(j)(2) is attached hereto in the form of a credit card form for the amount of $1120.00.

XV. Correspondence Information (37 C.F.R. § 1.740(a)(15)).

All inquiries and correspondence should be sent to:

Customer Number: 22850

Which corresponds to:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
1940 Duke Street
Alexandria, VA 22314

Telephone: 703-413-3000
Facsimile: 703-413-2220

XVI. Power of Attorney (37 C.F.R. §§ 1.730(a)(2) and (d)).

A copy of the original Power of Attorney is being submitted herewith as Exhibit F.

As can be seen from the face of the '458 patent itself, the '458 patent was originally assigned to Fujisawa Pharmaceutical Co., Ltd., of Osaka, Japan ("Fujisawa"). Effective April

1, 2005, Fujiswa became part of Astellas Pharma Inc., of Tokyo, Japan. A formal notice of the change of name has already been filed in the USPTO, and copies if the papers filed are attached hereto as Exhibit G. Oblon, Spivak, McClelland, Maier & Neustadt, P.C., remains the attorney of record for the '458 patent.

In view of the foregoing, Applicants submit that the present patent is entitled to the requested extension of patent term, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-506
NDA 21-754

Fujisawa Healthcare, Inc.
Attention: Mr. Robert M. Reed
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Mr. Reed:

Please refer to your new drug application (NDA) dated April 29, 2002, received April 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycamine™ (micafungin sodium) for Injection, 50 mg, NDA 21-506. The August 24, 2004 submission, received August 25, 2004, constituted a complete response to our January 29, 2003 approvable letter.

We acknowledge receipt of your submissions to NDA 21-506 dated:

October 1, 2004	December 23, 2004	February 9, 2005
October 15, 2004	January 6, 2005	February 11, 2005
October 20, 2004	January 10, 2005 (2)	February 15, 2005
October 25, 2004	January 26, 2005	February 28, 2005
October 29, 2004	January 27, 2005	March 8, 2005
November 12, 2004	February 2, 2005	March 9, 2005
December 1, 2004	February 3, 2005	March 10, 2005 (2)
December 22, 2004	February 4, 2005 (2)	

We also refer to your new drug application dated April 23, 2004, received April 26, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycamine™ (micafungin sodium) for Injection, 50 mg, NDA 21-754.

We acknowledge receipt of your submissions to NDA 21-754 dated:

May 11, 2004	December 22, 2004	February 4, 2005 (2)
August 24, 2004	December 23, 2004	February 11, 2005
September 22, 2004	January 6, 2005	February 18, 2005
October 1, 2004	January 10, 2005 (3)	February 22, 2005
October 20, 2004	January 26, 2005	February 28, 2005
November 12, 2004	January 27, 2005	March 8, 2005
November 18, 2004	February 2, 2005	March 9, 2005
December 1, 2004	February 3, 2005	March 10, 2005 (2)

These new drug applications provide for the use of Mycamine™ (micafungin sodium) for Injection, for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (NDA 21-506) and for the treatment of esophageal candidiasis (NDA 21-754).

We completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved NDAs 21-506 and 21-754.**" Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring the pediatric study requirement for ages 0 to 16 years for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation and for the treatment of esophageal candidiasis.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study under PREA for the prophylaxis of *Candida* infections in patients ages 0 to 16 years old undergoing hematopoietic stem cell transplantation,

2. Deferred pediatric study under PREA for the treatment of esophageal candidiasis in patients ages 0 to 16 years old.

Final Report Submissions: March 30, 2010

Submit final study reports to NDA 21-506 only. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-506 for this drug product, not to NDA 21-754. In the future, do not make submissions to NDA 21-754 except for the final printed labeling requested above.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Christina H. Chi, Ph.D., Regulatory Health Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:

1. text for the package insert,
2. immediate container
3. carton labels

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/s/

Edward Cox
3/16/05 12:54:49 PM
for Mark J. Goldberger, MD MPH

compounds within the scope of the claims. Ex parte Winters, 11 USPQ2d 1387 (Bd. Pat. App. & Int. 1988). Applicants submit that the compounds tested are representative of the scope of the compounds recited in Claim 20 since they are homologs. Therefore, it is respectfully requested that the rejection be withdrawn.

The rejection of Claims 1-19 under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patent 5,374,634, to Toshiro et al., is respectfully traversed.

This rejection is traversed based on the showing of unexpectedly superior antifungal properties of the claimed compounds. Additionally, this rejection is improper for Claims 23 and 30 and Claims 24-27, 32 and 34, since there is no disclosure or suggestion that R_1 is an aroyl substituted with a heterocyclic group in the specification or the claims of Toshiro et al. Therefore, it is respectfully requested that this rejection be withdrawn.

Applicants submit that the application is now in condition for allowance, and an early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No.: 24,618
Attorney of Record

Amy L. Hulina
Registration No.: 41,556

Fourth Floor
1755 Jefferson Davis Highway
Arlington Virginia 22202
Telephone No.: (703) 413-3000
Facsimile No.: (703) 413-2220

18-0971-0 PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

HIDENORI OHKI ET AL : EXAMINER: MARSHALL

SERIAL NO: 08/809,723 :

FILED: MAY 21, 1997 : GROUP ART UNIT: 1654

FOR: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY :

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

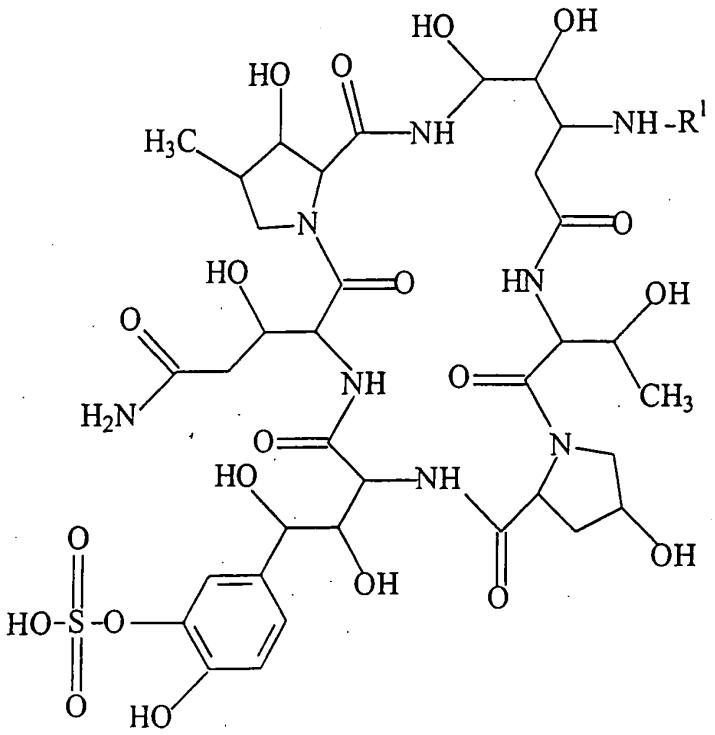
SIR:

Prior to examination please amend the above-identified application as follows:

IN THE CLAIMS

Cancel claims 20-36. Please add the following new claims:

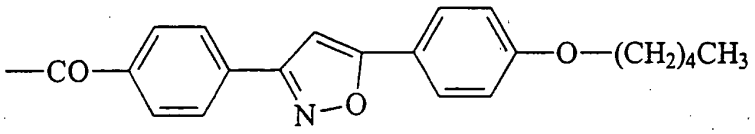
--37. A polypeptide compound of the following general formula (I):



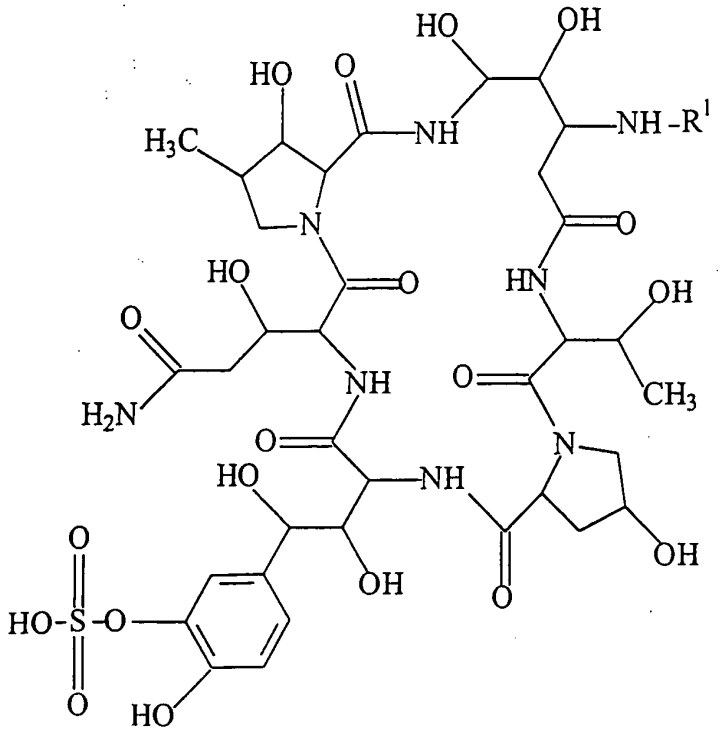
(I)

wherein R^1 is benzoyl substituted with isoxazolyl which has phenyl having lower alkoxy, or a salt thereof.

38. A compound of claim 37, wherein R^1 is



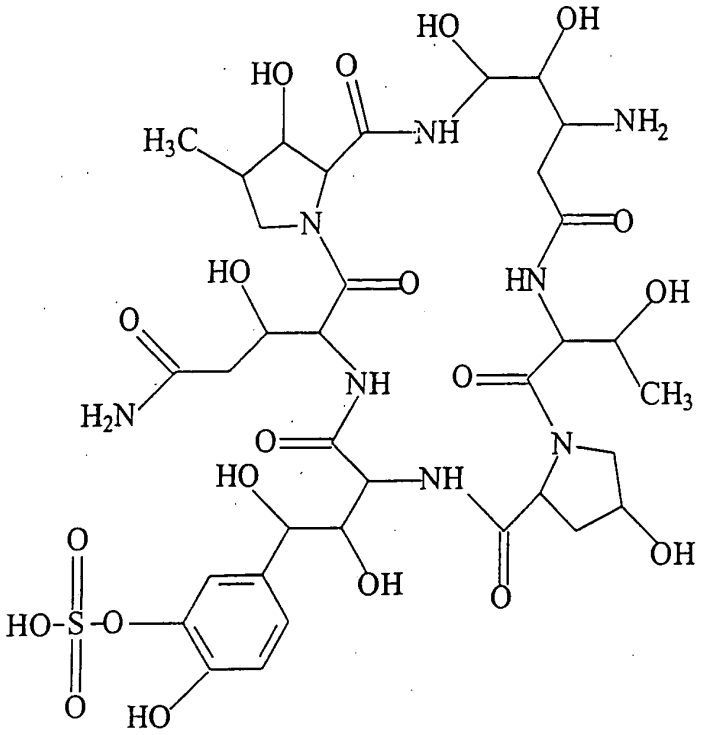
39. A process for the preparation of a polypeptide compound of the formula (I):



(I)

wherein R^1 is benzoyl substituted with isoxazolyl which has phenyl having lower alkoxy, or a salt thereof, said process comprising:

1) reacting a compound of the formula (II):



(II)

or its reactive derivative at the amino group or a salt thereof, with a compound of formula (III):

$$R^1\text{-}OH \qquad \text{(III)}$$

or its reactive derivative at the carboxy group or a salt thereof, wherein R^1 is defined above, to give a compound of formula (I).

40. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 37, or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or excipient.

41. A method for the therapeutic treatment of infectious diseases caused by pathogenic microorganisms, comprising administering an effective amount of a compound of claim 37 or a pharmaceutically acceptable salt thereof, to a human being or animal.--

REMARKS

Claims 37-41 are active in the application.

This case is a CPA of application serial No. 08/089723, in which a declaration was filed pursuant to 37 C.F.R. §1.132. The major issue in that case concerned whether the claims were commensurate in scope with data showing superior antifungal properties. The present claims are narrower, being directed to compounds in which R^1 is benzoyl substituted with a heterocycle which is itself substituted by phenyl having an alkoxy substitutent. These claims are commensurate in scope with data in the previously filed Rule 132 Declaration and the one submitted herewith (unexecuted) with data on the compound of Example 25 (claim 38).

Applicants submit that the case is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 24,618

Robert W. Hahl
Registration No. 33,893

Crystal Square Five - Fourth Floor
1755 Jefferson Davis Highway
Arlington, VA 22202
(703) 413-3000
Fax No.: (703) 413-2220
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Maintenance Fee Statement

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Patent Number: 6107458

Customer Number: 22850

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PATENT NUMBER	FEE AMT	SUR-CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
6,107,458	$910.00	$0.00	08/809,723	08/22/00	05/21/97	04	NO	PAID	18-971-0-PCT

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Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____.

☑ was filed as PCT international application

Number PCT/JP95/01983

on September 29, 1995,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
9420425.2	G. Britain	07/10/94	☑ Yes ☐ No
9508745.8	G. Britain	28/04/95	☑ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
PCT/JP95/01983	September 29, 1995	

And we (I) hereby appoint: Norman F. Oblon, Registration Number 24,618; Marvin J. Spivak, Registration Number 24,913; C. Irvin McClelland, Registration Number 21,124; Gregory J. Maier, Registration Number 25,599; Arthur I. Neustadt, Registration Number 24,854; Richard D. Kelly, Registration Number 27,757; James D. Hamilton, Registration Number 28,421; Eckhard H. Kuesters, Registration Number 28,870; Robert T. Pous, Registration Number 29,099; Charles L. Gholz, Registration Number 26,395; Vincent J. Sunderdick, Registration Number 29,004; William E. Beaumont, Registration Number 30,996; Steven B. Kelber, Registration Number 30,073; Robert F. Gnuse, Registration Number 27,295; Jean-Paul Lavalleye, Registration Number 31,451; Timothy R. Schwartz, Registration Number 32,171; Stephen G. Baxter, Registration Number 32,884; Martin M. Zoltick, Registration Number 35,745; Robert W. Hahl, Registration Number 33,893; Richard L. Treanor, Registration Number 36,379; Steven P. Weihrouch, Registration Number 32,829; John T. Goolkasian, Registration Number 26,142; Marc R. Labgold, Registration Number 34,651; William J. Healey, Registration Number 36,160; Richard L. Chinn, Registration Number 34,305; Steven E. Lipman, Registration Number 30,011; and Jacques M. Dulin, Registration Number 24,067; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Hidenori Ohki
NAME OF FIRST ~~SOLE~~ INVENTOR

Residence: 4-4-13-107, Nakasuji, Takarazuka-shi, HYOGO 665 JAPAN

Hidenori Ohki
Signature of Inventor

Citizen of: Japan

Post Office Address: the same as above

April 24, 1997
Date

Masaki Tomishima
NAME OF SECOND JOINT INVENTOR

Masaki Tomishima
Signature of Inventor

April 24, 1997
Date

Residence: 3-33-5, Gein, Minoo-shi, OSAKA 562 JAPAN

Citizen of: Japan

Post Office Address: the same as above

Akira Yamada
NAME OF THIRD JOINT INVENTOR

Akira Yamada
Signature of Inventor

April 24, 1997
Date

Residence: 4-8-30, Sawada, Fujiidera-shi, OSAKA 583 JAPAN

Citizen of: Japan

Post Office Address: the same as above

Hisashi Takasugi
NAME OF FOURTH JOINT INVENTOR

Hisashi Takasugi
Signature of Inventor

April 24, 1997
Date

Residence: 3-116-10, Mozu Umekita, Sakai-shi, OSAKA 591 JAPAN

Citizen of: Japan

Post Office Address: the same as above

NAME OF FIFTH JOINT INVENTOR

Signature of Inventor

Date

Residence:

Citizen of:

Post Office Address:

* * * COMMUNICATION RESULT REPORT (MAY. 9. 2005 11:32AM) * * *

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ATTORNEYS AT LAW
1940 DUKE STREET
ALEXANDRIA, VIRGINIA 22314
(703) 413-3000
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OBLONPAT@OBLON.COM
WWW.OBLON.COM

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Shaun Johnson

Total number of pages including this page: 27

Dept.: KLH
By: MJS/sli

OSMM&N File No. 270677US-18-18-0SD
Serial No. ____
Patent No. 5,376,634
6,107,458
6,265,536
In the matter of : FUJISAWA PHARMACEUTICAL CO., LTD.
For: Corporate Merger

- Credit Card Form for $120.00
- Commercial Register, Certified English Translation and Recordation Cover Sheet (PTO 1595) pages: 25

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E·H (E)

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06-04

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1. Name of conveying party(ies):
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Additional name(s) of conveying party(ies) attached? ☐ Yes ■ No

2. Name and address of receiving party(ies):
Name: ASTELLAS PHARMA INC.
Address: 3-11, Nihonbashi-Honcho 2-chome
Chuo-ku
Tokyo 103-8411
Japan

3. Nature of Conveyance:
☐ Assignment ■ Merger
☐ Security Agreement ☐ Change of Name
☐ Other
Execution Date: April 1, 2005

Additional name(s) and address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):
☐ This document is being filed together with a new application

A. Patent Application No.(s)

B. Patent No.(s)
5,376,634
6,107,458
6,265,536

Additional numbers attached? ☐ Yes ■ No

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6. Total applications and patents involved: 3

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Marvin J. Spivak
Name of Person Signing

Signature

5/9/05
Date

Registration Number: 24,913

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Phone 212/686-5555
Fax 212/686-5414

STATE OF NEW YORK)
CITY OF NEW YORK :
COUNTY OF NEW YORK)

CERTIFICATION

This is to certify that the following is, to the best of our knowledge and belief, a true and accurate translation into ENGLISH of the attached document(s) relating to:

Certificate of All Recorded Items in Commercial Register for Astellas Pharma Inc.

written in JAPANESE.

COPY

NEWTYPE COMMUNICATIONS, INC.

Sworn to and subscribed before me
this 6th day of May, 2005.

NOTARY PUBLIC

MICHAEL A. PRESTIA
Notary Public, State of New York
No. 01PR3157725
Qualified in Queens County
Commission Expires May 31, 2007

Certificate of All Recorded Items in Commercial Register

3-11 Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo-to
Astellas Pharma Inc.
Corporation, etc. No. 0199-01-034966

Trade name	Yamanouchi Pharmaceutical Co., Ltd.	
	Astellas Pharma Inc.	Change made April 1, 2005
		Registered April 1, 2005
Head office	3-11 Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo-to	
Publication method	Appearance in the Nihon Keizai Shimbun issued in Tokyo	
Access to information concerning balance sheet	http://www.yamanouchi.com/jp/index.html	Established March 25, 2003
		Registered April 1, 2003
	http://www.astellas.com/jp	Established April 1, 2005
		Registered April 1, 2005
Date of incorporation	March 20, 2002	
Purpose	1. Manufacture, sale, and import and export of pharmaceuticals, quasi-drugs, veterinary drugs, industrial chemicals, agricultural chemical, and other chemical products 2. Manufacture, sale, and import and export of food and food additives, condiments, feed and feed additives, cosmetics, hygiene items, medical devices, instrumentation, and miscellaneous everyday items 3. Manufacture, sale, and import and export of medical machinery and devices, industrial machinery and devices, and household machinery and devices 4. Manufacture, sale, and import and export of alcoholic beverages and beverage products 5. Raising, sale, and import and export of experimental animals 6. Buying and selling, leasing, management, and brokering of real estate 7. Warehousing and road transporting 8. Innkeeping and the management and administration of health and physical education facilities 9. Nonlife insurance agency business 10. Business of information processing services by computer 11. All business incidental to or related to the foregoing numbers	
	1. Manufacture, sale, and import and export of pharmaceuticals, quasi-drugs, veterinary drugs, reagents, industrial chemicals, agricultural chemical, and other chemical products 2. Manufacture, sale, and import and export of food and food additives, condiments, fertilizer, feed and feed additives, cosmetics, hygiene items, medical devices, veterinary medical devices, instrumentation, and miscellaneous everyday items 3. Buying and selling and import and export of natural products 4. Leasing and maintenance of medical devices 5. Manufacture, sale, import and export, leasing, and maintenance of medical machinery and devices, industrial machinery and devices, and household machinery and devices	

Reference No. u597415 * The underlined items have been expunged from the Register. 1/21

3-11 Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo-to
Astellas Pharma Inc.
Corporation, etc. No. 0199-01-034966

Splitting-off of company	Split off October 1, 2004 into Zepharma Co., Ltd., 7-1 Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo-to Registered October 1, 2004
Merger	Merger with Fujisawa Pharmaceutical Co., Ltd., 4-7 Doshomachi 3-chome, Chuo-ku, Osaka-shi Registered April 1, 2005
Matters concerning registration records	Pursuant to the provisions of 1989 Ministry of Justice Order No. 15, Supplementary Provisions, paragraph 3 Transcribed May 20, 1999

This is to certify that these are all the unclosed items recorded in the Register.

April 4, 2005

Tokyo Legal Affairs Bureau
Registrar: Motoyuki Oba (seal) [name partially obscured]

Reference No. u597415 *The underlined items have been expunged from the Register.

履歴事項全部証明書

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

商　号	山之内製薬株式会社	
	アステラス製薬株式会社	平成１７年　４月　１日変更 平成１７年　４月　１日登記
本　店	東京都中央区日本橋本町二丁目３番１１号	
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	ｈｔｔｐ：／／ｗｗｗ．ａｓｔｅｌｌａｓ．ｃｏｍ／ｊｐ	平成１７年　４月　１日変更 平成１７年　４月　１日登記
会社成立の年月日	昭和１４年３月２０日	
目　的	１．医薬品、医薬部外品、動物用医薬品、工業薬品、農薬その他化学的製品の製造、販売および輸出入 ２．食品および食品添加物、調味料、飼料および飼料添加物、化粧品、衛生用具、医療用具、計量器、日用品雑貨の製造、販売および輸出入 ３．医療用機械器具、産業用機械器具、家庭用機器の製造、販売および輸出入 ４．酒精飲料および飲料品の製造、販売および輸出入 ５．実験動物の飼育・販売および輸出入 ６．不動産の売買、賃貸借、管理およびその仲介 ７．倉庫業および道路運送事業 ８．旅館業および保健体育施設の経営および管理 ９．損害保険代理業 １０．コンピューターによる情報処理サービス業 １１．前各号に付帯または関連する一切の事業	
	１．医薬品、医薬部外品、動物用医薬品、試薬、工業薬品、農薬その他化学的製品の製造、販売および輸出入 ２．食品および食品添加物、調味料、肥料、飼料および飼料添加物、化粧品、衛生用具、医療用具、動物用医療用具、計量器、日用品雑貨の製造、販売および輸出入 ３．天産物の売買ならびに輸出入 ４．医療用具の賃貸借および保守 ５．医療用機械器具、産業用機械器具、家庭用機器の製造、販売、輸出入、賃貸借および保守	

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　

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	６．医療に関連する各種科学的検査 ７．酒類、酒精飲料および飲料品の製造、販売および輸出入 ８．実験動物の飼育・販売および輸出入 ９．不動産の売買、賃貸借、管理およびその仲介 １０．倉庫業、道路運送事業および貨物利用運送事業 １１．旅館業および保健体育施設の経営および管理 １２．損害保険代理業 １３．出版業 １４．コンピューターの販売、賃貸借および保守 １５．コンピューターのソフトウェアの開発、販売および賃貸借 １６．コンピューターによる情報処理・提供サービス業 １７．経営コンサルタント業 １８．前各号に付帯または関連する一切の事業 平成１７年　４月　１日変更　　平成１７年　４月　１日登記	
一単元の株式の数	１０００株	
	１００株	平成１４年　４月　１日変更 平成１４年　４月　２日登記
発行する株式の総数	８億株	
	２０億株	平成１７年　４月　１日登記
発行済株式の総数並びに種類及び数	発行済株式の総数 ３億６１１５万２５２２株	平成１３年　４月３０日変更 平成１３年　５月　９日登記
	発行済株式の総数 ３億６１２０万３０５２株	平成１４年　２月２８日変更 平成１４年　３月１１日登記
	発行済株式の総数 ３億６１２０万３６０４株	平成１４年　４月３０日変更 平成１４年　５月１０日登記
	発行済株式の総数 ３億６１２１万４２６２株	平成１４年　５月３１日変更 平成１４年　６月１２日登記
	発行済株式の総数 ３億６１２１万６４７０株	平成１４年１２月３０日変更 平成１５年　１月１４日登記

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	発行済株式の総数 ３億６１２２万１５２３株	平成１６年　４月３０日変更 平成１６年　５月１３日登記
	発行済株式の総数 ３億６１５４万９９７１株	平成１６年１０月３１日変更 平成１６年１１月１０日登記
	発行済株式の総数 ３億６１９５万４２１５株	平成１７年　１月３１日変更 平成１７年　２月　８日登記
	発行済株式の総数 ５億７１４２万８００３株	 平成１７年　４月　１日登記
資本の額	金９９６億９４５６万３８４１円	平成１３年　４月３０日変更 平成１３年　５月　９日登記
	金９９７億４４５６万３８４１円	平成１４年　２月２８日変更 平成１４年　３月１１日登記
	金９９７億４５５６万３５１３円	平成１４年　４月３０日変更 平成１４年　５月１０日登記
	金９９７億５６５６万３１８５円	平成１４年　５月３１日変更 平成１４年　６月１２日登記
	金９９７億６０５６万１８７３円	平成１４年１２月３０日変更 平成１５年　１月１４日登記
	金９９７億６５５６万１８７３円	平成１６年　４月３０日変更 平成１６年　５月１３日登記
	金１０００億９０５６万１８７３円	平成１６年１０月３１日変更 平成１６年１１月１０日登記
	金１００４億９０５６万１８７３円	平成１７年　１月３１日変更 平成１７年　２月　８日登記

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名義書換代理人の氏名及び住所並びに営業所	東京都港区芝三丁目３３番１号 中央三井信託銀行株式会社 東京都港区芝三丁目３３番１号 中央三井信託銀行株式会社　本店 平成１２年１２月　４日変更	平成１２年１２月　８日登記
役員に関する事項	取締役　小野田正愛	平成１３年　６月２８日重任
		平成１３年　７月１０日登記
		平成１５年　６月２７日退任
		平成１５年　７月１１日登記
	取締役　竹中登一	平成１３年　６月２８日重任
		平成１３年　７月１０日登記
	取締役　竹中登一	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	取締役　木村薫	平成１３年　６月２８日重任
		平成１３年　７月１０日登記
		平成１５年　６月２７日退任
		平成１５年　７月１１日登記
	取締役　柿谷宗敏	平成１３年　６月２８日重任
		平成１３年　７月１０日登記
		平成１５年　６月２７日退任
		平成１５年　７月１１日登記

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	取締役　髙山暢二	平成１３年　６月２８日重任
		平成１３年　７月１０日登記
	取締役　髙山暢二	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	取締役　河石清	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記
	取締役　上田英彦	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
	取締役　上田英彦	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　鈴木弘	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記
	取締役　能浦栄蔵	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記

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	取締役　井上雅勝	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記
	取締役　田村隼也	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
	取締役　田村隼也	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
	取締役　田村隼也	平成１６年　６月２４日重任
		平成１６年　７月　７日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	取締役　市川邦英	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
	取締役　市川邦英	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
	取締役　市川邦英	平成１６年　６月２４日重任
		平成１６年　７月　７日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	取締役　髙橋重一	平成１３年　６月２８日重任
		平成１３年　７月１０日登記
	取締役　髙橋重一	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記

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	取締役　畑中和義	平成１２年　６月２９日就任
		平成１２年　７月１２日登記
	取締役　畑中和義	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　石井康雄	平成１２年　６月２９日就任
		平成１２年　７月１２日登記
	取締役　石井康雄	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　佐羽俊男	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　佐羽俊男	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　岸　功	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　岸　功	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記

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	取締役　平岩廣章	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　平岩廣章	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　柳沢勲	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　柳沢勲	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
	取締役　柳澤勲	柳沢勲の氏
		平成１６年　３月１９日更正
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　臼田眞治	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　杉崎生弥	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　中島一	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。

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	取締役　宮崎石基	平成１５年　６月２７日就任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　吉長孝二	平成１５年　６月２７日就任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　長谷川忠夫	平成１５年　６月２７日就任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　松尾眞 （社外取締役）	平成１６年　６月２４日就任
		平成１６年　７月　７日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	取締役　青木初夫	平成１７年　４月　１日就任
		平成１７年　４月　１日登記
	取締役　竹中登一	平成１７年　４月　１日就任
		平成１７年　４月　１日登記
	取締役　田村隼也	平成１７年　４月　１日就任
		平成１７年　４月　１日登記
	取締役　野木森雅郁	平成１７年　４月　１日就任
		平成１７年　４月　１日登記
	取締役　市川邦英	平成１７年　４月　１日就任
		平成１７年　４月　１日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　

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	取締役　　瀬　島　宏　一	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　　児　島　章　郎 （社外取締役）	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　　松　尾　眞 （社外取締役）	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	千葉県流山市野々下三丁目９３１番地の３５ 代表取締役　　小　野　田　正　愛	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１４年　６月２７日辞任 平成１４年　７月１０日登記
	千葉県流山市松ケ丘四丁目５０５番地の５６ 代表取締役　　竹　中　登　一 東京都港区芝三丁目３４番１－１４０５号 代表取締役　　竹　中　登　一 東京都港区芝三丁目３４番１－１４０５号 代表取締役　　竹　中　登　一	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　３月１０日住所移転 平成１５年　３月１７日登記 平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日退任 平成１７年　４月　１日登記
	東京都中央区日本橋浜町二丁目３番２－１２０２号 代表取締役　　上　田　英　彦	平成１５年　６月２７日就任 平成１５年　７月１１日登記 平成１６年　６月２４日退任 平成１６年　７月　７日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　１０／２１

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会社法人等番号　０１９９－０１－０３４９６６

	埼玉県蓮田市緑町一丁目２１番１０号 代表取締役　田村隼也	平成１６年１０月　１日就任 平成１６年１０月　１日登記 平成１７年　３月３１日退任 平成１７年　４月　１日登記
	大阪府池田市畑四丁目１３番３号 代表取締役　青木初夫	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	東京都港区芝三丁目３４番１－１４０５号 代表取締役　竹中登一	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	埼玉県蓮田市緑町一丁目２１番１０号 代表取締役　田村隼也	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	大阪府高槻市真上町六丁目６５番２号 代表取締役　野木森雅郁	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	監査役　日巻洋之	平成１２年　６月２９日就任 平成１２年　７月１２日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	監査役　佐々木典夫 監査役　佐々木典夫	平成１２年　６月２９日就任 平成１２年　７月１２日登記 平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	監査役　立川四郎	平成１２年　６月２９日就任 平成１２年　７月１２日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　１１／２１

東京都中央区日本橋本町二丁目3番11号
アステラス製薬株式会社
会社法人等番号　0199－01－034966

	監査役　大谷豊達	平成13年　6月28日就任 平成13年　7月10日登記
	監査役　大谷豊達	平成16年　6月24日重任 平成16年　7月　7日登記
		平成17年　3月31日辞任 平成17年　4月　1日登記
	監査役　山田英夫	平成13年　6月28日就任 平成13年　7月10日登記
	監査役　山田英夫	平成16年　6月24日重任 平成16年　7月　7日登記
	監査役　斎藤健一郎	平成15年　6月27日就任 平成15年　7月11日登記
	監査役　松尾眞	平成15年　6月27日就任 平成15年　7月11日登記
		平成16年　6月24日辞任 平成16年　7月　7日登記
	監査役　石井政弥	平成17年　4月　1日就任 平成17年　4月　1日登記
	監査役　小林幹司	平成17年　4月　1日就任 平成17年　4月　1日登記
支店	1 東京都中央区日本橋本町二丁目4番7号	
	東京都中央区日本橋本町二丁目5番7号	平成14年　9月28日移転 平成14年10月　4日登記
	東京都中央区日本橋本町一丁目5番9号	平成17年　1月24日移転 平成17年　2月　1日登記

整理番号　ツ605098　　＊　下線のあるものは抹消事項であることを示す。　　12／21

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	2 大阪市中央区北浜三丁目７番１２号	
	大阪市中央区瓦町三丁目６番５号	平成１５年　５月１９日移転 平成１５年　５月２１日登記
	3 北海道札幌市中央区大通西五丁目９番地１	
	4 名古屋市中区栄一丁目１０番２１号	
	名古屋市中区丸の内二丁目１番３６号	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	5 宮城県仙台市青葉区大町二丁目２番２５号	
	6 福岡市博多区博多駅東一丁目１８番２５号	
	福岡市博多区下川端２番１号	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	7 東京都中央区日本橋本町二丁目５番６号	
	東京都中央区日本橋本町一丁目５番９号	平成１７年　１月３１日移転 平成１７年　２月　１日登記
	東京都台東区東上野五丁目２４番８号	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	8 香川県高松市寿町一丁目４番８号	
	香川県高松市サンポート２番１号	平成１６年　３月２２日移転 平成１６年　３月２２日登記
	9 広島県広島市中区大手町三丁目７番２号	
	広島市中区大手町二丁目１１番１０号	平成１７年　４月　１日移転 平成１７年　４月　１日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	１０ 台北市南京東路三段２８７号	平成１６年１０月３１日廃止 平成１６年１１月　１日登記
	１１ 横浜市中区太田町六丁目８４番地２ 横浜市西区みなとみらい二丁目２番１号	平成１５年　２月２５日移転 平成１５年　３月　４日登記
	１２ 京都市中京区烏丸通二条下る秋野々町５１３番地	
	１３ 東京都中央区日本橋本町二丁目５番６号 東京都中央区日本橋本町一丁目５番９号 さいたま市大宮区桜木町一丁目７番地５	平成１７年　１月３１日移転 平成１７年　２月　１日登記 平成１７年　４月　１日移転 平成１７年　４月　１日登記
	１５ 仙台市青葉区大町二丁目２番２５号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１６ 東京都台東区東上野五丁目２４番８号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１７ 千葉市美浜区中瀬二丁目６番地	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１８ 東京都中央区日本橋本町一丁目５番９号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	１９ 名古屋市中区丸の内二丁目１番３６号	平成１７年　４月　１日設置 平成１７年　４月　１日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	２０ 石川県金沢市本町一丁目５番２号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２１ 大阪市中央区瓦町三丁目６番５号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２２ 神戸市中央区磯辺通三丁目１番７号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２３ 岡山市下石井一丁目１番３号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２４ 福岡市博多区下川端２番１号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
新株予約権	第１回新株予約権 新株予約権の数 １４１０個 新株予約権の目的たる株式の種類及び数 当社普通株式　１４万１０００株 新株予約権１個当たりの目的たる株式の数（以下、「付与株式数」という。）は１００株とする。 なお、当社が当社普通株式の分割または併合を行う場合、次の算式により付与株式数を調整するものとし、調整の結果生じる１株未満の端数については、これを切り捨てるものとする。 調整後付与株式数　＝　調整前付与株式数　×　分割または併合の比率 また、当社が資本の減少、合併または会社分割を行う場合等、付与株式数の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で付与株式数を調整する。 各新株予約権の発行価額 無償	

各新株予約権の行使に際して払込みをすべき金額

各新株予約権の行使に際して払込みをなすべき金額は、各新株予約権の行使により発行または移転する株式１株当たりの払込金額（以下、「行使価額」という。）に付与株式数を乗じた金額とする。

行使価額は、新株予約権を発行する日（以下、「発行日」という。）の属する月の前月の各日（取引が成立しない日を除く。）の東京証券取引所における当社普通株式の普通取引の終値（以下、「終値」という。）の平均値とし、１円未満の端数は切り上げる。ただし、その金額が発行日の終値（当日に終値がない場合は、それに先立つ直近日の終値）を下回る場合は、当該終値を行使価額とする。

なお、発行日以降、当社が時価を下回る価額で、当社普通株式につき、新株式を発行または自己株式を処分する場合（新株予約権の行使及び「商法等の一部を改正する法律」（平成１３年法律第１２８号）の施行前の商法に基づく転換社債の転換の場合を除く。）次の算式により行使価額を調整し、調整により生ずる１円未満の端数は切り上げる。

$$\text{調整後行使価額} = \text{調整前行使価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新規発行株式数} \times \text{１株当たり払込金額}}{\text{時価}}}{\text{既発行株式数} + \text{新規発行株式数}}$$

上記の算式において、「既発行株式数」とは、当社の発行済株式数から当社が保有する自己株式数を控除した数とし、自己株式の処分を行う場合には、「新規発行株式数」を「処分する自己株式数」に読み替えるものとする。

また、発行日以降、当社が当社普通株式の分割または併合を行う場合には、行使価額は当該株式の分割または併合の比率に応じ比例的に調整されるものとし、調整により生ずる１円未満の端数は切り上げる。

さらに、発行日以降、当社が資本の減少、合併または会社分割を行う場合等、行使価額の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で行使価額を調整するものとする。

新株予約権を行使することができる期間

平成１７年７月１日から平成２５年６月２７日まで

新株予約権の行使の条件（払込価額及び行使期間を除く。）

各新株予約権の一部行使はできないこととする。

会社が新株予約権を消却することができる事由及び消却の条件

①当社が消滅会社となる合併契約書承認の議案が当社株主総会で承認された場合、または当社が完全子会社となる株式交換契約書承認の議案もしくは株式移転の議案につき当社株主総会で承認された場合は、当社は新株予約権を無償で消却することができるものとする。

②当社は、いつでも、当社が取得し保有する未行使の新株予約権を、無償にて消却することができるものとする。

平成１５年　７月１１日登記

第２回新株予約権
新株予約権の数
１４７０個

新株予約権の目的たる株式の種類及び数
当社普通株式１４万７０００株
新株予約権１個当たりの目的たる株式の数（以下、「付与株式数」という。）は１００株とする。
なお、当社が当社普通株式の分割または併合を行う場合、次の算式により付与株式数を調整するものとし、調整の結果生じる１株未満の端数については、これを切り捨てるものとする。
調整後付与株式数＝調整前付与株式数×分割または併合の比率
また、当社が資本の減少、合併または会社分割を行う場合等、付与株式数の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で付与株式数を調整する。
各新株予約権の発行価額
無償
各新株予約権の行使に際して払込みをすべき金額
各新株予約権の行使に際して払込みをなすべき金額は、各新株予約権の行使により発行または移転する株式１株当たりの払込金額（以下、「行使価額」という。）に付与株式数を乗じた金額とする。
行使価額は、新株予約権を発行する日（以下、「発行日」という。）の属する月の前月の各日（取引が成立しない日を除く。）の東京証券取引所における当社普通株式の普通取引の終値（以下、「終値」という。）の平均値とし、１円未満の端数は切り上げる。ただし、その金額が発行日の終値（当日に終値がない場合は、それに先立つ直近日の終値）を下回る場合は、当該終値を行使価額とする。
なお、発行日以降、当社が時価を下回る価額で、当社普通株式につき、新株式を発行または自己株式を処分する場合（新株予約権の行使、「商法等の一部を改正する法律」（平成１３年法律第１２８号）の施行前の商法に基づく転換社債の転換及び商法第２２１条ノ２の規定（単元未満株式の売渡請求）に基づく自己株式の譲渡の場合を除く。）は、次の算式により行使価額を調整し、調整により生ずる１円未満の端数は切り上げる。

$$\text{調整後行使価額} = \text{調整前行使価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新規発行株式数} \times \text{１株当たり払込金額}}{\text{時価}}}{\text{既発行株式数} + \text{新規発行株式数}}$$

上記の算式において、「既発行株式数」とは、当社の発行済株式数から当社が保有する自己株式数を控除した数とし、自己株式の処分を行う場合には、「新規発行株式数」を「処分する自己株式数」に読み替えるものとする。
また、発行日以降、当社が当社普通株式の分割または併合を行う場合には、行使価額は当該株式の分割または併合の比率に応じ比例的に調整されるものとし、調整により生ずる１円未満の端数は切り上げる。
さらに、発行日以降、当社が資本の減少、合併または会社分割を行う場合等、行使価額の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で行使価額を調整するものとする。
新株予約権を行使することができる期間
平成１８年７月１日から平成２６年６月２４日まで
新株予約権の行使の条件（払込価額及び行使期間を除く。）
各新株予約権の一部行使はできないこととする。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	会社が新株予約権を消却することができる事由及び消却の条件 ①当社が消滅会社となる合併契約書承認の議案が当社株主総会で承認された場合、または当社が完全子会社となる株式交換契約書承認の議案もしくは株式移転の議案につき当社株主総会で承認された場合は、当社は新株予約権を無償で消却することができるものとする。 ②当社は、いつでも、当社が取得し保有する未行使の新株予約権を、無償にて消却することができるものとする。 平成１６年　７月　７日登記
転換社債	第３回無担保転換社債 転換社債の総額 金１４９億２１００万円 金１４９億１５００万円 平成１３年　４月３０日変更　平成１３年　５月　９日登記 金１４９億１３００万円 平成１４年　４月３０日変更　平成１４年　５月１０日登記 金１４９億１１００万円 平成１４年　５月３１日変更　平成１４年　６月１２日登記 金１４９億３００万円 平成１４年１２月３０日変更　平成１５年　１月１４日登記 転換の条件 転換により発行する株式１株の発行価額（以下転換価額という。）は、下記(1)によって決定し、転換により発行すべき株式数は、次のとおりとする。ただし、本社債額面金額の一部及び利息については、転換を請求することはできない。 株式数＝各社債権者が転換請求のため提出した本社債額面金額の総額 ／ 転換価額 この場合に、１株未満の端数を生じたときは、その端数に相当する社債額面金額は、額面１００円につき１００円の割合で償還する。 (1)　転換価額　金４４１３円 (2)　転換価額の調整 転換価額は、当社が本社債発行後、時価を下回る払込金額で新株式を発行する場合には、次の算式により調整される。 調整後転換価額 ＝ 調整前転換価額 × (既発行株式数 ＋ 新発行株式数 × １株当りの払込金額 ／ 時価) ／ (既発行株式数＋新発行株式数) なお、株式配当、無償交付、株式の分割もしくは併合等が行われる場合にも調整されるものとする。ただし、転換により当社記名式額面普通株式を発行する場合で、調整後の転換価額が当社記名式額面普通株式の額面金額を下回るときは、当該額面金額を転換価額とする。 転換によって発行すべき株式の内容 当社記名式額面普通株式（１株の額面金額５０円） ただし、本社債の転換により発行する株式を当社記名式無額面普通株式とした場合は、当社記名式無額面普通株式。

東京都中央区日本橋本町二丁目３番１１号
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	転換の請求をすることのできる期間 昭和６２年９月１日から昭和７７年１２月３０日まで 各転換社債の金額 金１００万円 各転換社債につき払い込んだ金額 全額 本社債はこれを株式に転換することができる
	平成１４年１２月３０日転換請求期間満了 平成１５年　１月１４日登記
	２０１４年満期円貨建転換社債 転換社債の総額 金１８８億８０００万円 金１８６億８０００万円 平成１１年　５月３１日変更　平成１１年　６月１４日登記 金１７６億９０００万円 平成１１年　６月３０日変更　平成１１年　７月１２日登記 金１１２億３０００万円 平成１１年　７月３１日変更　平成１１年　８月１０日登記 金１０５億４０００万円 平成１１年　８月３１日変更　平成１１年　９月１３日登記 金９６億５０００万円 平成１１年１０月３１日変更　平成１１年１１月１２日登記 金９４億４０００万円 平成１１年１１月３０日変更　平成１１年１２月１３日登記 金９２億２０００万円 平成１１年１２月３１日変更　平成１２年　１月１４日登記 金９１億８０００万円 平成１２年　１月３１日変更　平成１２年　２月１４日登記 金８３億９０００万円 平成１２年　２月２９日変更　平成１２年　３月１４日登記 金８１億５０００万円 平成１２年　４月３０日変更　平成１２年　５月１２日登記 金８１億４０００万円 平成１２年　５月３１日変更　平成１２年　６月１３日登記 金７５億１０００万円 平成１２年　７月３１日変更　平成１２年　８月　８日登記 金７２億９０００万円 平成１２年　８月３１日変更　平成１２年　９月１１日登記 金６６億４０００万円 平成１２年１１月３０日変更　平成１２年１２月　８日登記 金６６億１０００万円 平成１２年１２月３１日変更　平成１３年　１月１２日登記 金６６億円 平成１３年　１月３１日変更　平成１３年　２月　８日登記 金６５億円 平成１４年　２月２８日変更　平成１４年　３月１１日登記 金６４億８０００万円 平成１４年　５月３１日変更　平成１４年　６月１２日登記

	金６４億７０００万円 平成１６年　４月３０日変更　平成１６年　５月１３日登記 金５８億２０００万円 平成１６年１０月３１日変更　平成１６年１１月１０日登記 金５０億２０００万円 平成１７年　１月３１日変更　平成１７年　２月　８日登記 転換の条件 本社債は、その額面金額に対し、下記の転換価額につき当社額面普通株式１株の割合をもって当社額面普通株式に転換することができる。 但し、転換の際に生じる１株未満の端数は、これを切り捨て、現金による調整は原則として行わない。 イ．当初の転換価額は、１株当り金１９７９円とする。 ロ．転換価額の修正 １９９８年３月３１日、２００４年３月３１日及び２００９年３月３１日（以下それぞれ「決定日」という。）より東京証券取引所における当社額面普通株式の普通取引の終値のある４５連続営業日前に開始する３０連続営業日における終値の平均値に１．０２５を乗じ１円未満を切り上げた額が、当該各決定日に有効な転換価額を１円以上下回る場合には、転換価額は１９９８年４月２２日、２００４年４月２２日及び２００９年４月２２日（以下それぞれ「効力発生日」という。）以降、上記により算出された各金額（但し、決定日から効力発生日の前日までに効力の発生した下記ハ．の調整を受ける。）に修正されるものとする。但し、転換価額は、かかる修正の結果として当初の転換価額（但し、下記ハ．の調整がなされた場合には、調整後の金額）の５０％未満に修正されることはなく、５０％未満となる場合は、かかる転換価額の５０％にあたる金額の１円未満を切り上げた価額とする。 ハ．転換価額の調整 転換価額は、当社が本社債発行後、当社の普通株式の時価を下回る払込金額で新たに普通株式を発行する場合、次の算式により調整される。 $$\text{調整後転換価額} = \text{調整前転換価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新発行株式数} \times \text{１株当り払込金額}}{\text{１株当り時価}}}{\text{既発行株式数} + \text{新発行株式数}}$$ 又、転換価額は、株式の分割・併合、当社の普通株式の時価を下回る当初転換価額又は新株引受権行使価額での転換社債又は新株引受権付社債の発行その他一定の場合にも適宜調整される。但し、転換価額は当社額面普通株式の額面金額を下回らないものとする。 転換によって発行すべき株式の内容 当社額面普通株式（現在の１株の額面金額５０円） 転換の請求をすることのできる期間 １９９４年５月９日から２０１４年３月２４日の営業終了時（転換請求地時間）までとする。 各転換社債の金額 金１０００万円 各転換社債につき払い込んだ金額 全額 本社債はこれを株式に転換することができる。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

会社分割	平成１６年１０月１日東京都中央区日本橋本町二丁目７番１号ゼファーマ株式会社に分割 平成１６年１０月　１日登記
吸収合併	大阪市中央区道修町三丁目４番７号藤沢薬品工業株式会社を合併 平成１７年　４月　１日登記
登記記録に関する事項	平成元年法務省令第１５号附則第３項の規定により 平成１１年　５月２０日移記

これは登記簿に記録されている閉鎖されていない事項の全部であることを証明した書面である。

平成１７年　４月　７日
東京法務局
登記官　大　庭　元　行

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　２１／２１

Preparation 43

O^4-Octyl-N,N-dimethyl-L-tyrosine methyl ester
IR (Neat): 2930, 2860, 1730, 1250 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 1.26 (10H, m), 1.68 (2H, m), 2.80 (2H, m), 3.33 (6H, s), 3.37 (1H, m), 3.53 (3H, s), 3.89 (2H, t, J=6.4 Hz), 6.79 (2H, d, J=8.6 Hz), 7.08 (2H, d, J=8.6 Hz)

Preparation 44

Methyl (4-octyloxyphenyl)glyoxylate
IR (Neat): 2930, 2850, 1730, 1670, 1600, 1260, 1210, 1160 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.3 Hz), 1.2–1.5 (10H, m), 1.6–1.9 (2H, m), 3.93 (3H, s), 4.10 (2H, t, J=6.8 Hz), 7.12 (2H, d, J=8.9 Hz), 7.92 (2H, d, J=8.9 Hz)

The following compounds (Preparations 45 to 51) were obtained according to a similar manner to that of Preparation 4.

Preparation 45

4-(2-Butoxyethoxy)benzoic acid
IR (Nujol): 1670, 1610, 1260 cm^{-1}
NMR (DMSO-d_6, δ): 0.87 (3H, t, J=7.2 Hz), 1.2–1.6 (4H, m), 3.45 (2H, t, J=6.4 Hz), 3.70 (2H, t, J=4.4 Hz), 4.16 (2H, t, J=4.4 Hz), 7.02 (2H, d, J=8.9 Hz), 7.88 (2H, d, J=8.9 Hz), 12.63 (1H, s)

Preparation 46

2-(4-Octyloxyphenyl)acetic acid
IR (Nujol): 1680, 1240, 820, 780 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.1–1.5 (10H, m), 1.6–1.8 (2H, m), 3.47 (2H, s), 3.92 (2H, t, J=6.4 Hz), 6.84 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.6 Hz)

Preparation 47

3-(4-Octyloxyphenyl)propionic acid
IR (Nujol): 1680, 1500, 1200 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.3 Hz), 1.1–1.5 (10H, m), 1.6–1.8 (2H, m), 2.47 (2H, t, J=7.2 Hz), 2.74 (2H, t, J=7.2 Hz), 3.90 (2H, t, J=6.4 Hz), 6.81 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.6 Hz), 12.10 (1H, br s)

Preparation 48

2-(4-Octyloxyphenyl)-2-methoxyacetic acid
IR (Nujol): 1760, 1720, 1600, 1500, 1240, 1180, 1100, 830 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 2.6–2.8 (2H, m), 3.26 (3H, s), 3.94 (2H, t, J=6.4 Hz), 4.67 (1H, s), 6.90 (2H, d, J=8.6 Hz), 7.27 (2H, d, J=8.6 Hz)

Preparation 49

O^4-Octyl-N-(t-butoxycarbonyl)-D-tyrosine
IR (Nujol): 3400, 2900, 1700, 1500, 1240, 1160 cm^{-1}
NMR (DMSO-d_6, δ): 0.859 (3H, t, J=6.8 Hz), 1.20–1.30 (10H, m), 1.32 (9H, s), 1.68 (2H, m), 2.67–2.95 (1H, m), 3.90 (2H, t, J=7 Hz), 4.01 (1H, m), 6.81 (2H, d, J=8.6 Hz), 7.02 (1H, d, J=8.3 Hz), 7.13 (2H, d, J=8.6 Hz)

Preparation 50

O^4-Octyl-N,N-dimethyl-L-tyrosine
IR (Neat): 2940, 2860, 2600, 1620, 1240 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 1.26 (10H, m), 1.68 (2H, m), 2.67 (6H, s), 2.8–3.6 (3H, m), 3.91 (2H, t, J=6.4 Hz), 6.85 (2H, d, J=8.5 Hz), 7.16 (2H, d, J=8.5 Hz)

Preparation 51

O^4-Octyloxyphenyl)glyoxylic acid
IR (Neat): 1730, 1670, 1600, 1260, 1160 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1–65–1.85 (2H, m), 4.09 (2H, t, J=6.5 Hz), 7.12 (2H, d, J=8.9 Hz), 7.89 (2H, d, J=8.9 Hz)

Preparation 52

N^T-Octyl-N-(t-butoxycarbonyl)-L-histidine was obtained from N-(t-butoxycarbonyl)-L-histidine methyl ester according to similar manners to those of Preparations 3 and 4.
NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.3 Hz), 1.23 (10H, m), 1.35 (9H, s), 2.83 (2H, m), 3.90 (2H, t, J=7 Hz), 4.0–4.2 (1H, m), 6.36 (1H, s), 7.02 (1H, d, J=8 Hz), 7.75 (1H, s)

The following compounds (Preparations 53 to 60) were obtained according to a similar manner to that of Preparation 11.

Preparation 53

4-Octyloxyphthalic acid
IR (Neat): 2930, 2860, 2500, 1700, 1600, 1260 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.5–1.8 (2H, m), 4.05 (2H, t, J=6.2 Hz), 7.03 (1H, d, J=2.6 Hz), 7.06 (1H, dd, J=8.4 Hz and 2.6 Hz), 7.72 (1H, d, J=8.4 Hz)

Preparation 54

3-Methoxy-4-octyloxybenzoic acid
IR (Nujol): 2600, 1680, 1600, 1270, 1230 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 3.80 (3H, s), 4.01 (2H, t, J=6.5 Hz), 7.03 (1H, d, J=8.5 Hz), 7.44 (1H, d, J=1.9 Hz), 7.54 (1H, dd, J=8.5 Hz and 1.9 Hz)

Preparation 55

4-(4-Octyloxyphenyl)benzoic acid
IR (Nujol): 1670, 1600, 830, 770 cm^{-1}
NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 4.01 (2H, t, J=6.4 Hz), 7.04 (2H, d, J=8.8 Hz), 7.68 (2H, d, J=8.8 Hz), 7.75 (2H, d, J=8.5 Hz), 7.99 (2H, d, J=8.5 Hz)

Preparation 56

6-(2-Ethylhexyloxy)-2-naphthoic acid
IR (Nujol): 1660, 1610, 1280, 1200 cm^{-1}
NMR (DMSO-d_6, δ): 0.88 (3H, t, J=7.3 Hz), 0.92 (3H, t, J=7.3 Hz), 1.2–1.6 (8H, m), 1.7–1.9 (1H, m), 4.01 (2H, d, J=5.7 Hz), 7.23 (1H, dd, J=8.9 and 2.4 Hz), 7.4 2 (1H, d, J=2.4 Hz), 7.86 (1H, d, J=8.7 Hz), 7 .94 (1H, d, J=8.7 Hz), 8.01 (1H, d, J=8.9 Hz), 8.51 (1H, s), 12.9 (1H, s)

Preparation 57

6-(3,7-Dimethyl-6-octenyloxy)naphthoic acid
IR (Nujol): 1660, 1610, 1290, 1200 cm^{-1}
NMR (DMSO-d_6, δ): 0.95 (3H, d, J=6.1 Hz), 1.1–1.5 (2H, m), 1.57 (3H, s), 1.64 (3H, s), 1.6–2.1 (5H, m), 4.15 (2H, t, J=6.7 Hz), 5.10 (1H, t, J=7.1 Hz), 7.22 (1H, dd, J=8.9 Hz and 2.3 Hz), 7.42 (1H, d, J=2.3 Hz), 7.86 (1H, d, J=8.6 Hz), 7.94 (1H, d, J=8.6 Hz), 8.01 (1H, d, J=8.9 Hz), 8.52 (1H, s), 12.89 (1H, s)

Preparation 58

6-(3 7-Dimethyl-2,6-octadienyloxy)naphthoic acid
IR (Nujol): 1660, 1620, 1210 cm^{-1}
NMR (DMSO-d_6, δ): 1.57 (3H, s), 1.60 (3H, s), 1.76 (3H, s), 2.07 (4H, m), 4.70 (2H, d, J=6.5 Hz), 5.07 (1H, m), 5.51 (1H, t, J=6.5 Hz), 7.24 (1H, dd, J=8.9 Hz and 2.4 Hz), 7.41 (1H, d, J=2.4 Hz), 7.85 (1H, d, J=8.7 Hz), 7.94 (1H, d, J=8.7 Hz), 8.01 (1H, d, J=8.9 Hz), 8.52 (1H, s), 12.88 (1H, s)

Preparation 59

(2E)-3-(4-Octyloxyphenyl)acrylic acid
IR (Nujol): 1660, 1600, 1240 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.2-1.5 (10H, m), 1.6-1-8 (2H, m), 4.00 (2H, t, J=6.4 Hz), 6.36 (1H, d, J=16 Hz), 6.95 (2H, d, J=8.7 Hz), 7.54 (1H, d, J=16 Hz), 7.61 (2H, d, J=8.7 Hz), 12.20 (1H, br s)

Preparation 60

Sodium 6-octyloxy-2-naphthalene sulfonate
IR (Nujol): 1230, 1180, 860, 820 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6 Hz), 1.1-1.6 (10H, m), 4.06 (2H, t, J=5 Hz), 7.08 (1H, d, J=9 Hz), 7.21 (1H, s), 7.79 (1H, d, J=9 Hz), 8.00 (1H, s)

Preparation 61

To a solution of thionyl chloride (0.692 ml) and N,N-dimethylformamide (0.022 ml) was added sodium 6-octyloxy-2-naphthalenesulfonate (1 g) under ice-cooling and stirred for 1.5 hours at 95° C. The reaction mixture was evaporated under reduced pressure to give 6-octyloxy-2-naphthylsulfonyl chloride (1 g).
IR (Nujol): 1610, 1260, 1160 cm^{-1}
NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.2 Hz), 1.2-1.7 (10H, m), 1.8-2.0 (2H, m), 4.12 (2H, t, J=6.5 Hz), 7.20 (1H, d, J=2.2 Hz), 7.32 (1H, dd, J=9.0 Hz and 2.2 Hz), 7.84-7.97 (3H, m), 8.49 (1H, s)

The following compounds (Preparations 62 to 63 to 71) were obtained according to a similar manner to that of Preparation 12.

Preparation 62

1-(4-Octylbenzoyl)-1H-benzotriazole-3-oxide
IR (Neat): 2930, 2850, 1780, 1610, 1240, 990 cm^{-1}

Preparation 63

1-[4-(4-Octyloxyphenyl)benzoyl]-1H-benzotriazole-3-oxide
IR (Nujol): 1770, 1600, 980 cm^{-1}

Preparation 64

1-[6-(2-Ethylhexyloxy)-2-naphthoyl]-1H-benzotriazole-3-oxide
IR (Nujol): 1770, 1620, 1270, 1180 cm^{-1}
NMR ($CDCl_3$, δ): 0.93 (3H, t, J=7.1 Hz), 0.98 (3H, t, J=7.4 Hz), 1.3-1.7 (8H, m), 1.7-2.0 (1H, m), 4.03 (2H, d, J=5.7 Hz), 7.22 (1H, d, J=2.2 Hz), 7.29 (1H, dd, J=8.9 Hz, 2.2 Hz), 7.4-7.7 (3H, m), 7.87 (1H, d, J=9.5 Hz), 7.92 (1H, d, J=9.5 Hz), 8.1-8.2 (2H, m), 8.80 (1H, s)

Preparation 65

1-[6-(3,7-Dimethyl-6-octenyloxy)-2-naphthoyl]-1H-benzotriazole-3-oxide
IR (Neat): 2900, 1770, 1620, 1180 cm^{-1}

Preparation 66

1-[6-{(E)-3,7-Dimethyl-2,6-octadienyloxy}-2-naphthoyl]-1H-benzotriazole-3-oxide
IR (Nujol): 1770, 1620, 1270, 1180 cm^{-1}

Preparation 67

1-(2-Anthrylcarbonyl)-1H-benzotriazole-3-oxide
IR (Nujol): 1780, 1200, 720, 740 cm^{-1}

Preparation 68

1-[2-(4-Octyloxyphenyl)acetyl]-1H-benzotriazole-3oxide
IR (Nujol): 1730, 1460, 1420, 1250, 1130 cm^{-1}

Preparation 69

1-[3-(4-Octyloxyphenyl)propionyl]-1H-benzotriazole-3-oxide
IR (Nujol): 1730, 1420, 1340, 1240, 950 cm^{-1}

Preparation 70

1-[(E)-3-(4-Octyloxyphenyl)acryloyl]-1H-benzotriazole-3-oxide
IR (Nujol): 1770, 1600, 1260, 1080 cm^{-1}

Preparation 71

1-(O^4-Octyl-N,N-dimethyl-L-tyrosyl)-1H-benzotriazole-3-oxide
IR (Neat): 2930, 2850, 1800, 1610 cm^{-1}

Preparation 72

To a suspension of lithium aluminum hydride (4.05 g) in tetrahydrofuran (475 ml) was added dropwise a solution of 4-octyloxybenzaldehyde (25 g) in tetrahydrofuran (25 ml) at 55°~60° C. The reaction mixture was stirred under reflux for 1 hour, and thereto was added sodium fluoride (35.84 g) and water (11.52 ml) under ice-cooling. The mixture was stirred for 30 minutes, and filtrated. The filtrate was evaporated in vacuo to give 4-octyloxybenzyl alcohol (25.1 g) as crystals.
IR (Nujol): 3200, 1605, 1510 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.26-1.38 (10H, m), 1.62-1.72 (2H, m), 3.92 (2H, t, J=6.5 Hz), 4.40 (2H, d, J=5.7 Hz), 5.03 (1H, t, J=5.7 Hz), 6.85 (2H, d, J=8.6 Hz), 7.20 (2H, d, J=8.6 Hz)

Preparation 73

To a suspension of 4-octyloxybenzyl alcohol (25 g), N-hydroxyphthalimide (17.15 g) and triphenylphosphine (27.74 g) in tetrahydrofuran (250 ml) was added dropwise diethyl azodicarboxylate (18.4 g) under ice-cooling. The reaction mixture was stirred at room temperature for 2 hours, and evaporated in vacuo. The residue was purified by chromatography on silica gel to give N-(4-octyloxybenzyloxy)phthalimide (33.45 g) as crystals.
IR (Nujol): 1780, 1725, 1605, 1580, 1505 cm^{-1}
NMR (DMSO-d_6, δ): 0.86 (3H, m), 1.26 (10H, m), 1.70 (2H, m), 3.95 (2H, t, J=6.5 Hz), 5.08 (2H, s), 6.93 (2H, d, J=8.6 Hz), 7.40 (2H, d, J=8.6 Hz), 7.85 (4H, s)

Preparation 74

To a solution of N-(4-octyloxybenzoyloxy)phthalimide (4.13 g) in tetrahydrofuran (16 ml) was added hydrazine-hydrate (0.53 ml) at room temperature. After the mixture was stirred at the same temperature for 1 hour, the precipitate was filtered off. To the filtrate was added water (6 ml) and 4-hydroxyphenylglyoxylic acid (1.5 g) at room temperature. The mixture was main-

tained at pH 4~4.5 with aqueous sodium bicarbonate solution for 2 hours, thereto was added ethyl acetate, and adjusted to pH 2 with 1N hydrochloric acid. The separated organic layer was washed with brine, and dried over magnesium sulfate. The organic solvent was evaporated in vacuo to give (4-hydroxyphenyl)-2-(4-octyloxybenzyloxyimino)acetic acid (3.4 g).

IR (Nujol): 3400, 1715, 1605, 1590, 1505 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, m), 1.25 (10H, m), 1.69 (2H, m), 3.94 (2H, t, J=6.4 Hz), 5.07 (2H, s), 6.82 (2H, d, J=8.7 Hz), 6.90 (2H, d, J=8.6 Hz), 7.29 (2H, d, J=8.6 Hz), 7.35 (2H, d, J=8.7 Hz)

The following compounds (Preparations 75 and 76) were obtained according to a similar manner to that of Preparation 74.

Preparation 75

2-Phenyl-2-(4-octyloxybenzyloxyimino)acetic acid

IR (Nujol): 1720, 1610, 1585, 1515 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.26 (10H, m), 1.69 (2H, m), 3.94 (2H, t, J=6.5 Hz), 5.13 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.22–7.49 (7H, m)

Preparation 76

2-(4-Octyloxybenzyloxyimino)acetic acid

IR (Nujol): 1700, 1670, 1600 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.2 Hz), 1.26 (10H, m), 1.70 (2H, m), 3.95 (2H, t, J=6.5 Hz), 5.13 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.29 (2H, d, J=8.6 Hz), 7.56 (1H, s)

Preparation 77

A solution of 4-octyloxyphenylglyoxylic acid (0.935 g) in a mixture of water (9 ml) and tetrahydrofuran (18 ml) and adjusted to pH 3.5–4 with 1N hydrochloric acid and methoxyamine hydrochloride (0.337 g) was added thereto at room temperature. The mixture was stirred for 2 hours at room temperature maintaining pH 3.5~4 with 1N hydrochloric acid. The reaction mixture was added to ethyl acetate. The organic layer was separated and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 2-(4-octyloxyphenyl)-2-methoxyiminoacetic acid (0.57 g).

IR (Nujol): 1700, 1600, 1250, 1030 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.3 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 3.89 (3H, s), 3.99 (2H, t, J=6.4 Hz), 7.00 (2H, d, J=8.9 Hz), 7.45 (2H, d, J=8.9 Hz), 14.05 (1H, s)

Preparation 78

To a mixture of 2,3,4,5,6-pentafluorobenzoic acid (1 g) and 2,2,3,3,4,4,5,5-octafluoropentanol (1.18 g) in N,N-dimethylformamide (5 ml) was added 62% sodium hydride (0.39 g) at room temperature. The mixture was stirred at the same temperature for 1 hour, and thereto was added a mixture of water and ethyl acetate. The separated organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by chromatography on silica gel to give 4-(2,2,3,3,4,4,5,5-octafluoropentyloxy)-2,3,5,6-tetrafluorobenzoic acid (923.0 mg).

IR (Nujol): 1700, 1580 cm^{-1}

NMR (DMSO-d_6, δ): 4.96 (2H, t, J=14.2 Hz), 7.10 (1H, tt, J=5.6 Hz and 50.2 Hz)

Preparation 79

4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluorooctyloxy)-2,3,5,6-tetrafluorobenzoic acid

IR (Nujol): 3400, 1640, 1560 cm^{-1}

NMR (DMSO-d_6, δ): 4.95 (2H, t, J=14.0 Hz)

The following compounds (Preparations 80 to 90) were obtained according to a similar manner to that of Preparation 5.

Preparation 80

Succinimido 2-(4-hydroxyphenyl)-2-(4-octyloxybenzyloxyimino)acetate

IR (Nujol): 1800, 1770, 1700, 1600 cm^{-1}

Preparation 81

Succinimido 2-Phenyl-2-(4-octyloxybenzyloxyimino-)acetate

IR (Nujol): 1780, 1730, 1605 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, m), 1.26 (10H, m), 1.69 (2H, m), 2.90 (4H, m), 3.94 (2H, t, J=6.4 Hz), 5.30 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.25–7.56 (7H,

Preparation 82

Succinimido 2-(4-Octyloxybenzyloxyimino)acetate

IR (Nujol) 1760, 1725, 1600, 1580 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.26 (10H, m), 1.70 (2H, m), 2.85 (4H, s), 3.96 (2H, m), 5.28 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.33 (2H, d, J=8.6 Hz), 8.12 (1H, s)

Preparation 83

Succinimido 4-(2,2,3,3,4,4,5,5-octafluoropentyloxy)-2,3,5,6-tetraflurobenzoate

IR (Nujol): 3500, 1770, 1740, 1640 cm^{-1}

NMR (DMSO-d_6, δ): 2.90 (4H, s), 5.23 (2H, t, J=13.8 Hz), 7.11 (1H, tt, J=50.2 Hz and 5.6 Hz)

Preparation 84

Succinimido 4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyloxy)-2,3,5,6-tetrafluorobenzoate

IR (Nujol): 1735, 1620, 1600 cm^{-1}

NMR (DMSO-d_6, δ): 2.90 (4H, s), 5.12 (2H, t, J=13.8 Hz)

Preparation 85

Succinimido 3-methoxy-4-octyloxybenzoate

IR (Nujol): 1760, 1730, 1600, 1280, 1200, 880 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.6–1.9 (2H, m), 2.88 (4H, s), 3.84 (3H, s), 4.09 (2H, t, J=6.5 Hz), 7.19 (1H, d, J=8.6 Hz), 7.49 (1H, d, J=2.0 Hz), 7.73 (1H, dd, J=8.6 and 2.0 Hz)

Preparation 86

Succinimido 4-(2-butoxyethoxy)benzoate

IR (Nujol): 1730, 1600, 1250, 1060 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=7.2 Hz), 1.2–1.6 (4H, m), 2.89 (4H, s), 3.46 (2H, t, J=6.3 Hz), 3.73 (2H, t, J=4.4 Hz), 4.25 (2H, t, J=4.4 Hz), 7.18 (2H, d, J=9.0 Hz), 8.04 (2H, d, J=9.0 Hz)

Preparation 87

Succinimido 2-(4-octyloxyphenyl)-2-methoxyacetate

IR (Nujol): 1810, 1740, 1610, 1250, 1210, 1100 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 2.80 (4H, s), 3.35 (3H, s), 3.97 (2H, t, J=6.4 Hz), 5.35 (1H, s), 6.96 (2H, d, J=S.7 Hz), 7.38 (2H, d, J=8.7 Hz)

Preparation 88

O^4-Octyl-N-(t-butoxycarbonyl)-D-tyrosine succinimido ester

IR (Nujol): 3370, 1780, 1730, 1700, 1250, 1200 cm^{-1}

Preparation 89

Succinimido 2-(4-octyloxyphenyl)-2-methoxyiminoacetate

IR (Nujol): 1800, 1780, 1730, 1600, 1250, 1180, 1130 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz) 1.2-1.5 (10H, m), 1.6-1.8 (2H, m), 2.89 (4H, s), 4.01 (3H, s), 4.03 (2H, t, J=6.4 Hz), 7.08 (2H, d, J=8.9 Hz), 7.68 (2H, d, J=8.9 Hz)

Preparation 90

N^{τ}-Octyl-N-(t-butoxycarbonyl)-L-histidine succinimido ester

IR (Neat): 1810, 1780, 1730, 1500, 1360, 1200, 1160 cm^{-1}

Preparation 91

4-Octyloxyphthalic anhydride was obtained from 4-octyloxyphthalic acid according to a similar manner to that of Preparation 5.

IR (Neat): 2910, 2850, 1840, 1760, 1640, 1610, 1290, 1260 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2-1.5 (10H, m), 1.6-1.9 (2H, m), 4.19 (2H, t, J=6.5 Hz), 7.47 (1H, dd, J=8.4 Hz and 2.2 Hz), 7.57 (1H, d, J=2.2 Hz), 7.98 (1H, d, J=8.4 Hz)

Preparation 92

N-Octyloxycarbonyloxysuccinimide was obtained according to a similar manner to that of Preparation 5.

IR (Neat): 2960, 2850, 1780, 1740, 1260, 1230 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.2-1.4 (10H, m), 1.6-1.8 (2H, m), 2.84 (4H, s), 4.32 (2H, t, J=6.7 Hz)

Preparation 93

To a solution of octyl phenyl ether (1.53 g) in chloroform (6 ml) was added chlorosulfonic acid at 0° C. The mixture was stirred at room temperature for 30 minutes, then the mixture was poured into a mixture of water and tetrahydrofuran.

The separated organic layer was washed with sodium chloride aqueous solution, dried over magnesium sulfate and then the solvent was evaporated in vacuo. The residue was subjected to a column chromatography on silica gel to give 4-octyloxyphenylsulfonyl chloride (1.25 g).

IR (Nujol): 1600, 1580, 1500, 1380, 1180 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.6 Hz), 1.20-1.50 (10H, m), 1.80 (2H, m), 4.06 (2H, t, J=6.4 Hz), 7.03 (2H, d, J=9.0 Hz), 7.96 (2H, d, J=9.0 Hz)

The following compounds (Preparations 94 and 95) were obtained according to a similar manner to that of Preparation 5.

Preparation 94

Succinimido 4-(4-heptyloxyphenyl)benzoate

IR (Nujol): 1760, 1740, 1600 cm^{-1}

NMR ($CDCl_3$, δ): 0.87 (3H, t, J=6.8 Hz), 1.2-1.7 (8H, m), 1.7-1.9 (2H, m), 2.92 (4H, s), 4.01 (2H, t, J=6.5 Hz), 7.00 (2H, d, J=8.8 Hz), 7.58 (2H, d, J=8.8 Hz), 7.69 (2H, d, J=8.5 Hz), 8.17 (2H, d, J=8.5 Hz)

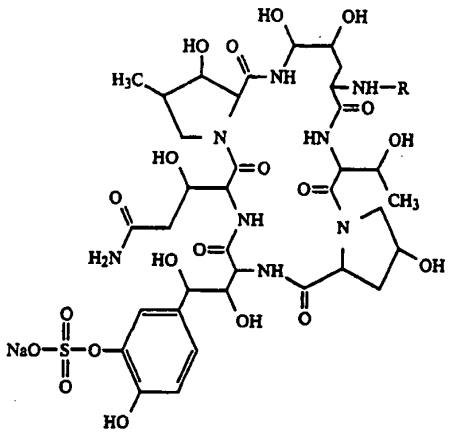
Preparation 95

Succinimido 4-(4-hexyloxyphenoxy)benzoate

IR (Nujol): 1760, 1120, 1600 cm^{-1}

NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.8 Hz), 1.2-1.5 (6H, m), 1.7-1.9 (2H, m), 2.90 (4H, s), 3.96 (2H, t, J=6.5 Hz), 6.9-7.1 (6H, m), 8.07 (2H, d, J=9 Hz)

In the following, the structures of the compounds of Examples 13 to 53 are shown (SEQ ID NO: 1).



In the following formulae, ^{t}Bu means t-butyl, and p-TsOH means p-toluenesulfonic acid.

Example No.	Compound No.	R
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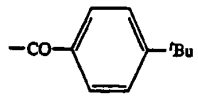
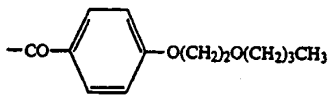
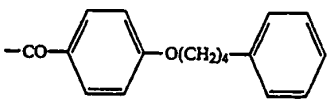
14	FR139537	
15	FR141145	
16	FR139538	

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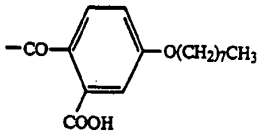
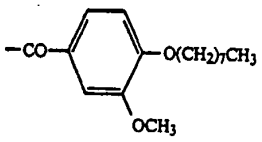
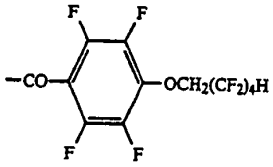
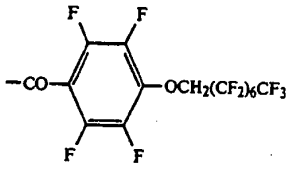
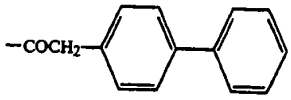
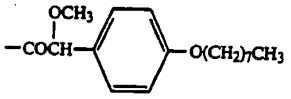
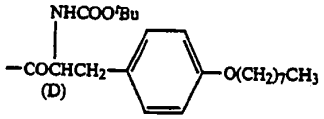
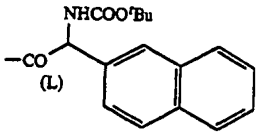
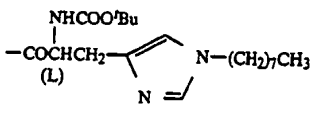
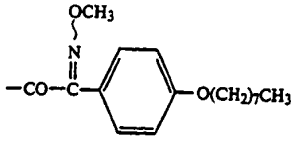
Example No.	Compound No.	R
17	FR140215	
18	FR140216	
19	FR140727	
20	FR143301	
21	FR140495	
22	FR139503	
23	FR139500	
24	FR139501	
25	FR139502	
26	FR138959	

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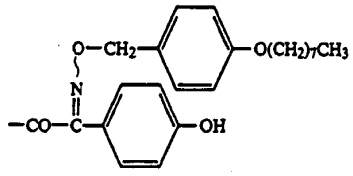
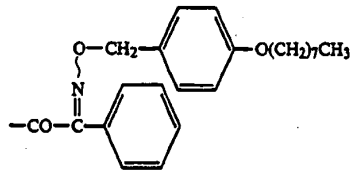
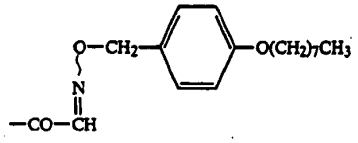
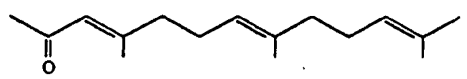
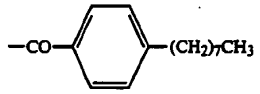
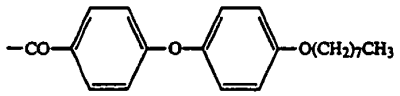
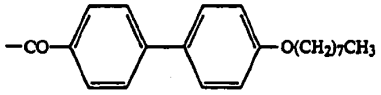
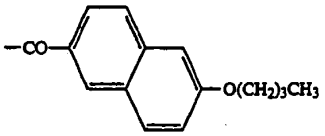
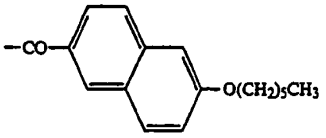
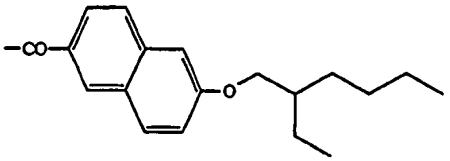
Example No.	Compound No.	R
27	FR140291	
28	FR141580	
29	FR141579	
30	FR141146	
31	FR140731	
32	FR140217	
33	FR142472	
34	FR140496	
35	FR140497	
36	FR143483	

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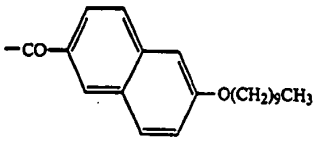
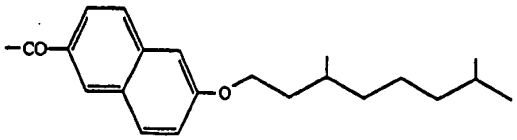
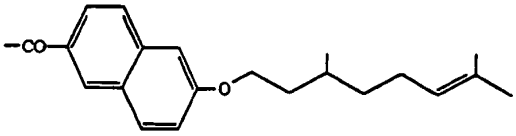
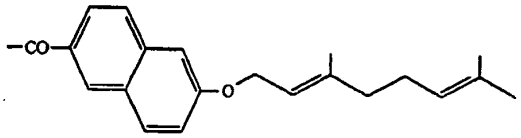
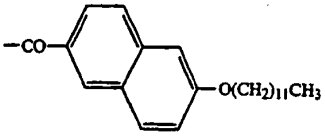
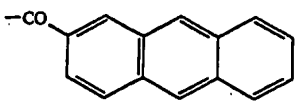
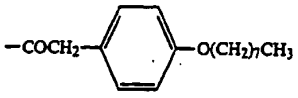
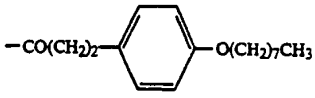
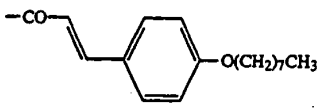
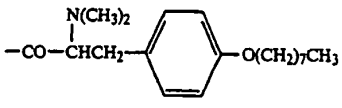
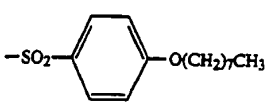
Example No.	Compound No.	R
37	FR140728	
38	FR142172	
39	FR143326	
40	FR142390	
41	FR140729	
42	FR140730	
43	FR143020	
44	FR143021	
45	FR141315	
46	FR140105	
47	FR141564	

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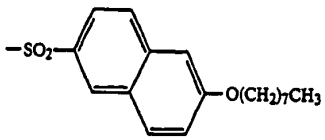
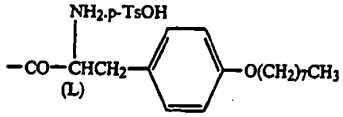
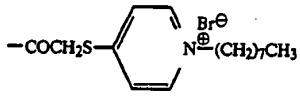
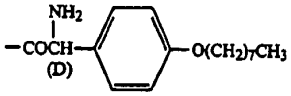
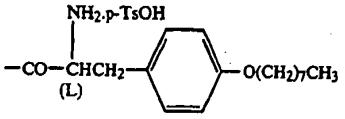
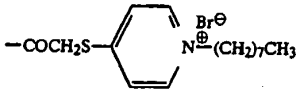
Example No.	Compound No.	R
48	FR143170	
49	FR138912	
50	FR138960	
51	FR138727	
52	FR138912	
53	FR138960	

EXAMPLE 13

FR139835 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with N-octyloxycarbonyloxysuccinimide according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

FAB-MS e/z=1137 (M+Na)

EXAMPLE 14

FR139537 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 4-t-butylbenzoate according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (D_2O, δ): 1.05 (3H, d, J=6.9 Hz), 1.15 (3H, d, J=5.9 Hz), 1.33 (9H, s), 2.0–2.3 (3H, m), 2.4–2.6 (3H, m), 2.7–2.9 (1H, m), 3.4–3.6 (1H, m), 3.8–4.9 (12H, m), 5.07 (2H, m), 5.40 (1H, d, J=3 Hz), 7.06 (1H, d, J=8.2 Hz), 7.08 (1H, dd, J=8.2 Hz and 2 Hz), 7.27 (1H, d, J=2 Hz), 7.60 (1H, d, J=8.6 Hz), 7.75 (1H, d, J=8.6 Hz)

EXAMPLE 15

FR141145 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 4-(2-butoxyethoxy)benzoate according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (DMSO-d_6, +D_2O, δ): 0.88 (3H, t, J=7.3 Hz), 0.96 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.7 Hz), 1.2–1.6 (4H, m), 1.7–2.0 (3H, m), 2.1–2.65 (4H, m), 3.16 (1H, m), 3.7–4.5 (20H, m), 4.78 (1H, d, J=3 Hz), 4.86 (1H, d, J=3.8 Hz), 5.02 (1H, d, J=3 Hz), 6.74 (1H, d, J=8.2 Hz), 6.79 (1H, d, J=8.2 Hz), 7.00 (2H, d, J=8.9 Hz), 7.06 (1H, s), 7.87 (2H, d. J=8.9 Hz)

FAB-MS e/z=1201 (M+Na)

EXAMPLE 16

FR139538 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 4-(4-phenylbutoxy)benzoate according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

FAB-MS e/z=1233 (M+Na)

EXAMPLE 17

FR140215 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 4-octyloxyphthalic anhydride according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

FAB-MS e/z=1257 (M+Na)

EXAMPLE 18

FR140216 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 3-methoxy-4-octyloxybenzoate according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

FAB-MS e/z=1243 (M+Na)

EXAMPLE 19

FR140727 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 4-(2,2,3,3,4,4,5,5-octafluoropentyloxy)-

2,3,5,6-tetrafluorobenzoate according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1630 cm^{-1}

FAB-MS e/z: 1387 (M+Na)

EXAMPLE 20

FR143301 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyloxy)-2,3,5,6-tetrafluorobenzoate according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1630 cm^{-1}

FAB-MS e/z=1534 (M+)

EXAMPLE 21

FR140495 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 2-(4-biphenylyl)acetate according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (CD_3OD, δ): 1.0–1.1 (6H, m), 1.9–2.2 (3H, m), 2.3–2.6 (3H, m), 2.7–2.85 (1H, m), 3.35 (1H, m), 3.58 (2H, s), 3.65–4.7 (13H, m), 4.93 (1H, d, J=3 Hz), 5.04 (1H, d, J=3.8 Hz), 5.25 (1H, d, J=3 Hz), 6.85 (1H, d, J=8.3 Hz), 7.01 (1H, dd, J=8.3 Hz and 2 Hz), 7.3–7.6 (10H, m)

EXAMPLE 22

FR139503 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 2-(4-octyloxyphenyl)-2-methoxyacetate according to a similar manner to that of Example 3.

IR (Nujol): 3330, 1620 cm^{-1}

FAB-MS e/z=1257 (M+Na)

EXAMPLE 23

FR139500 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with O^4-octyl-N-(t-butoxycarbonyl)-D-tyrosine succinimido ester according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (CD_3OD, δ): 0.90 (3H, t, J=6.8 Hz), 1.06 (3H, d, J=6.8 Hz), 1.17 (3H, d, J=6.7 Hz), 1.20–1.30 (10H, m), 1.35 (9H, s), 1.74 (2H, m), 1.9–2.1 (3H, m), 2.45 (3H, m), 2.76 (1H, m), 3.0–3.1 (1H, m), 3.37 (1H, m), 3.7–4.6 (18H, m), 4.94 (1H, d, J=3 Hz), 5.01 (1H, d, J=3.8 Hz), 5.25 (1H, d, J=3 Hz), 6.79 (2H, d, J=8.5 Hz), 6.83 (1H, d, J=8.3 Hz), 7.03 (1H, dd, J=8.3 Hz and 2 Hz), 7.12 (2H, d, J=8.8 Hz), 7.31 (1H, d, J=2 Hz)

EXAMPLE 24

FR139501 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with N-(t-butoxycarbonyl)-L-2-(2-naphthyl)glycine succinimido ester according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

EXAMPLE 25

FR139502 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with N^t-octyl-N-(t-butoxycarbonyl)-L-histidine succinimido ester according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

FAB-MS e/z=1330 (M+Na)

EXAMPLE 26

FR138959 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 2-(4-octyloxyphenyl)-2-methoxyiminoacetate according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (CD_3OD, δ): 0.91 (3H, t, J=6.6 Hz), 1.06 (3H, d, J=6.8 Hz), 1.25 (3H, d, J=6.3 Hz), 1.25–1.6 (10H, m), 1.65–1.9 (2H, m), 1.9–2.2 (3H, m), 2.3–2.65 (3H, m), 1.75–1.9 (1H, m), 3.3–3.5 (1H, m), 3.95 (3H, s), 3.7–4.75 (16H, m), 5.03 (1H, d, J=3.0 Hz), 5.11 (1H, d, J=3.7 Hz), 5.46 (1H, d, J=2.7 Hz), 6.86 (1H, d, J=8.2 Hz), 6.89 (2H, d, J=8.9 Hz), 7.01 (1H, dd, J=8.2 Hz and 2 Hz), 7.31 (1H, d, J=2 Hz), 7.54 (2H, d, J=8.9 Hz)

FAB-MS e/z=1270 (M+Na)

EXAMPLE 27

FR140291 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 2-(4-hydroxyphenyl)-2-(4-octyloxybenzyloxyimino)acetate according to a similar manner to that of Example 3.

IR (Nujol): 3250, 1650, 1620 cm^{-1}

FAB-MS e/z=1363 (M+Na)

EXAMPLE 28

FR141580 substance (SEQ ID NO. 1) was obtained by reacting FR133303 substance (SEQ ID NO. 1) with succinimido 2-phenyl-2-(4-octyloxybenzyloxyimino-)acetate according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1646 cm^{-1}

FAB-MS e/z=1346 (M+Na)

EXAMPLE 29

FR141579 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with succinimido 2-(4-octyloxybenzyloxyimino)acetate according to a similar manner to that of Example 3.

IR (Nujol): 3250, 1650 cm^{-1}

FAB-MS e/z=1270 (M+Na)

EXAMPLE 30

FR141146 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[(2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienoyl]-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620, 1040 cm^{-1}

NMR (CD_3OD, δ): 1.06 (3H, d, J=6.8 Hz), 1.19 (3H, d, J=5.9 Hz), 1.60 (3H, s), 1.62 (3H, s), 1.66 (3H, s), 1.9–2.2 (11H, m), 2.05 (3H, s), 2.3–2.6 (3H, m), 2.7–2.9 (1H, m), 3.35 (1H, m), 3.7–5.0 (14H, m), 5.08 (4H, m), 5.27 (1H, d, J=2.8 Hz), 5.77 (1H, s), 6.86 (1H, d, J=8.3 Hz), 7.04 (1H, dd, J=8.3 Hz and 1.9 Hz), 7.32 (1H, d, J=1.9 Hz)

EXAMPLE 31

FR140731 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-(4-octylbenzoyl)-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620, 1040 cm^{-1}

NMR (CD_3OD, δ): 0.86 (3H, t, J=6.8 Hz), 1.06 (3H, d, J=6.8 Hz), 1.21 (3H, d, J=5.8 Hz), 1.25–1.45 (10H, m), 1.55–1.75 (2H, m), 1.9–2.25 (3H, m), 2.35–2.6 (3H, m), 2.65 (2H, t, J=7.5 Hz), 2.81 (1H, m), 3.32 (1H, m), 3.7–4.8 (14H, m),4.98 (1H, d, J=3 Hz), 5.09 (1H, d,

J=3.9 Hz), 5.31 (1H, d, J=3 Hz), 6.86 (1H, d, J=8.3 Hz), 7.03 (1H, dd, J=8.3 Hz and 2 Hz), 7.24 (2H, d, J=8.2 Hz), 7.33 (1H, d, J=2 Hz), 7.74 (2H, d, J=8.2 Hz)

FAB-MS e/z=1197 (M+Na)

EXAMPLE 32

FR140217 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[4-(4-octyloxy)phenoxy]benzoyl-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620 cm^{-1}

FAB-MS e/z=1305 (M+Na)

EXAMPLE 33

FR142472 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[4-(4-octyloxyphenyl)benzoyl]-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (CD_3OD, δ): 0.88 (3H, t, J=6.7 Hz), 1.06 (3H, d, J=6.8 Hz), 1.23 (3H, d, J=6.1 Hz), 1.3–1.6 (10H, m), 1.8–1.9 (2H, m), 1.9–2.3 (3H, m), 2.3–2.7 (3H, m), 2.9–3.0 (1H, m), 3.39 (1H, m), 3.7–4.7 (16H, m), 4.99 (1H, d, J=3.0 Hz), 5.10 (1H, d, J=3.7 Hz), 5.35 (1H, d, J=2.7 Hz), 6.87 (1H, d, J=8.3 Hz), 6.99 (2H, d, J=8.8 Hz), 7.04 (1H, dd, J=8.3 Hz and 1.9 Hz), 7.33 (1H, d, J=1.9 Hz), 7.58 (2H, d, J=8.8 Hz), 7.62 (2H, d, J=8.4 Hz), 7.87 (2H, d, J=8.4 Hz)

FAB-MS e/z=1289 (M+Na)

EXAMPLE 34

FR140496 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-(6-butoxy-2-naphthoyl)-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620 cm^{-1}

FAB-MS e/z=1207 (M+Na)

EXAMPLE 35

FR140497 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-(6-hexyloxy-2-naphthoyl)-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (DMSO-d_6+D_2O, δ): 0.89 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.9 Hz), 1.08 (3H, d, J=5.9 Hz), 1.2–1.6 (6H, m), 1.7–2.1 (5H, m), 2.1–2.5 (3H, m), 2.5–2.7 (1H, m), 3.19 (1H, m), 3.73 (2H, m), 3.8–4.5 (12H, m), 4.80 (1H, d, J=3 Hz), 4.88 (1H, d, J=3.8 Hz), 5.08 (1H, d, J=3 Hz), 6.74 (1H, d, J=8.2 Hz), 6.80 (1H, dd, J=8.2 Hz and 2 Hz), 7.08 (1H, d, J=2 Hz), 7.26 (1H, dd, J=8.9 Hz and 2.4 Hz), 7.39 (1H, d, J=2.4 Hz), 7.85 (1H, d, J=8.7 Hz), 7.89 (1H, d, J=8.7 Hz), 7.93 (1H, d, J=8.9 Hz), 8.44 (1H, s)

FAB-MS e/z=1236 (M+Na)

EXAMPLE 36

FR143483 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[6-(2-ethylhexyloxy)-2-naphthoyl]-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3250, 1620 cm^{-1}

NMR (CD_3OD, δ): 0.93 (3H, t, J=7.4 Hz), 0.98 (3H, t, J=7.4 Hz), 1.06 (3H, d, J=6.8 Hz), 1.24 (3H, d, J=6.0 Hz), 1.3–1.7 (8H, m), 1.7–1.9 (1H, m), 1.9–2.3 (3H, m), 2.3–2.7 (3H, m), 2.8–3.0 (1H, m), 3.39 (1H, m), 3.7–4.7 (16H, m), 5.00 (1H, d, J=4.4 Hz), 5.11 (1H, d, J=3.7 Hz), 5.37 (1H, d, J=2.6 Hz), 6.87 (1H, d, J=8.3 Hz), 7.04 (1H, dd, J=8.3 Hz and 2 Hz), 7.17 (1H, dd, J=8.9 Hz and 1.9 Hz), 7.22 (1H, d, J=2 Hz), 7.33 (1H, d, J=1.9 Hz), 7.7–7.9 (3H, m), 8.29 (1H, s)

FAB-MS e/z=1263 (M+Na)

EXAMPLE 37

FR140728 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-(6-decyloxy-2-naphthoyl)-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (DMSO-d_6+D_2O, δ): 0.86 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.9 Hz), 1.2–1.6 (14H, m), 1.7–2.1 (5H, m), 2.1–2.5 (3H, m), 2.5–2.7 (1H, m), 3.19 (1H, m), 3.45 (1H, m), 3.73 (2H, m), 3.9–4.5 (12H, m), 4.79 (1H, d, J=3 Hz), 4.87 (1H, d, J=3.8 Hz), 5.07 (1H, d, J=3 Hz), 6.74 (1H, d, J=8.2 Hz), 6.79 (1H, dd, J=8.1 Hz and 2 Hz), 7.06 (1H, d, J=2 Hz), 7.23 (1H, dd, J=8.9 Hz and 2.4 Hz), 7.38 (1H, J=2.4 Hz), 7.85 (1H, d, J=8.7 Hz), 7.89 (1H, J=8.7 Hz), 7.93 (1H, d, J=8.9 Hz), 8.45 (1H, s)

FAB-MS e/z=1291 (M+Na)

EXAMPLE 38

FR142172 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[6-(3,7-dimethyloctyloxy)-2-naphthoyl]-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1610 cm^{-1}

NMR (DMSO-d_6+D_2O, δ): 0.85 (6H, d, J=6.6 Hz), 0.95 (3H, d, J=5.9 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.1–1.4 (6H, m), 1.4–2.1 (7H, m), 2.1–2.5 (3H, m), 2.5–2.7 (1H, m), 3.19 (1H, m), 3.74 (2H, m), 3.9–4.6 (12H, m), 4.81 (1H, d, J=3 Hz), 4.87 (1H, d, J=3.8 Hz), 5.07 (1H, d, J=3 Hz), 6.74 (1H, d, J=8.2 Hz), 6.83 (1H, dd, J=8.1 Hz and 2 Hz), 7.06 (1H, d, J=2 Hz), 7.23 (1H, dd, J=8.9 Hz and 2.4 Hz), 7.40 (1H, d, J=2.4 Hz), 7.85 (1H, d, J=8.7 Hz), 7.89 (1H, d, J=8.7 Hz), 7.93 (1H, d, J=8.9 Hz), 8.45 (1H, s)

FAB-MS e/z=1291 (M+Na)

EXAMPLE 39

FR143326 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[6-(3,7-dimethyl-6-octenyloxy)-2-naphthoyl]-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620, 1260, 1040 cm^{-1}

NMR (CD_3OD, δ): 1.00 (3H, d, J=6.2 Hz), 1.06 (3H, d, J=6.8 Hz), 1.25 (3H, d, J=5.9 Hz), 1.2–1.6 (2H, m), 1.61 (3H , s), 1.67 (3H, s), 1.63–2.3 (8H, m), 2.3–2.7 (3H, m), 2.8–3.0 (1H, m), 3.39 (1H, m), 3.7–4.8 (16H, m), 5.00 (1H, d, J=5.1 Hz), 5.08–5.2 (2H, m), 5.37 (1H, d, J=2.5 Hz), 6.87 (1H, d, J=8.3 Hz), 7.04 (1H, d, J=8.3 Hz), 7.15 (1H, d, J=8.9 Hz), 7.21 (1H, s), 7.33 (1H, s), 7.71 (1H, d, J=8.7 Hz), 7.77–7.85 (2H, m), 8.28 (1H, s)

EXAMPLE 40

FR142390 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[6-{(E)-3,7-dimethyl-2,6-octadienyloxy}-2-naphthoyl]-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (DMSO-d_6+D_2O, δ): 0.97 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=6.0 Hz), 1.57 (3H, s), 1.61 (3H, s), 1.76 (3H, s), 1.8–2.5 (9H, m), 2.5–2.7 (1H, m), 3.19 (1H, m), 3.45 (1H, m), 3.73 (2H, m), 3.9–4.6 (11H, m), 4.70 (2H, d, J=6.5 Hz), 4.80 (1H, d, J=3 Hz), 4.87 (1H, d, J=3.8 Hz), 5.07 (2H, m), 5.51 (1H, t, J=6.5 Hz), 6.74 (1H, d, J=8.3 Hz), 6.83 (1H, dd, J=8.3 Hz and 2 Hz), 7.07 (1H, d, J=2 Hz), 7.24 (1H, dd, J=8.9 Hz and 2.4 Hz), 7.40 (1H, d, J=2.4 Hz), 7.8–8.0 (3H, m), 8.45 (1H, s)

FAB-MS e/z=1287 (M+Na)

EXAMPLE 41

FR140729 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-(6-dodecyloxy-2-naphthoyl)-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1610 cm^{-1}

NMR (DMSO-d_6+D_2O, δ): 0.85 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.9 Hz), 1.2–1.6 (18H, m), 1.7–2.1 (5H, m), 2.1–2.5 (3H, m), 2.5–2.7 (1H, m), 3.19 (1H, m), 3.45 (1H, m), 3.73 (2H, m), 3.9–4.5 (12H, m), 4.79 (1H, d, J=3 Hz), 4.87 (1H, d, J=3.8 Hz), 5.07 (1H, d, J=3 Hz), 6.74 (1H, d, J=8.1 Hz), 6.78 (1H, dd, J=8.1 Hz and 2 Hz), 7.06 (1H, d, J=2 Hz), 7.23 (1H, dd, J=8.9 Hz and 2.4 Hz), 7.38 (1H, d, J=2.4 Hz), 7.85 (1H, d, J=8.7 Hz), 7.89 (1H, d, J=8.7 Hz), 7.93 (1H, d, J=8.9 Hz), 8.44 (1H, s)

FAB-MS e/z=1320 (M+Na)

EXAMPLE 42

FR140730 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-(2-anthrylcarbonyl)-1H-benzotriazole-3oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 162.0 cm^{-1}

FAB-MS e/z=1.185 (M+Na)

EXAMPLE 43

FR143020 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[2-(4-octyloxyphenyl)acetyl]-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (CD_3OD, δ): 0.87 (3H, t, J=6.8 Hz), 1.0–1.2 (6H, m), 1.2–1.6 (10H, m), 1.6–1.85 (2H, m), 1.85–2.1 (3H, m), 2.3–2.6 (3H, m), 2.7–2.85 (1H, m), 3.32 (1H, m), 3.46 (2H, s), 3.7–4.7 (16H, m), 5.04 (1H, d, J=3.7 Hz), 5.23 (1H, d, J=2.7 Hz), 6.75–6.9 (3H, m), 7.01 (1H, d, J=8.3 Hz), 7.15 (2H, d, J=8.5 Hz), 7.30 (1H, s)

FAB-MS e/z=1227 (M+Na)

EXAMPLE 44

FR143021 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[3-(4-octyloxyphenyl)propionyl]-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 162.0 cm^{-1}

FAB-MS e/z=1241 (M+Na)

EXAMPLE 45

FR141315 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-[(E)-3-(4-octyloxyphenyl)acryloyl]-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (DMSO-d_6+D_2O, δ): 0.86 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.4 Hz), 1.2–1.5 (10H, m), 1.6–2.0 (5H, m), 2.1–2.5 (3H, m), 2.5–2.6 (1H, m), 3.17 (1H, m), 3.3–4.5 (15H, m), 4.79 (1H, d, J=3 Hz), 4.86 (1H, d, J=3.8 Hz), 5.01 (1H, d, J=3 Hz), 6.57 (1H, d, J=15.8 Hz), 6.74 (1H, d, J=8.2 Hz), 6.82 (1H, d, J=8.2 Hz), 6.97 (2H, d, J=8.8 Hz), 7.09 (1H, s), 7.34 (1H, d, J=15.8 Hz), 7.52 (2H, d, J=8.8 Hz)

FAB-MS e/z=1239 (M+Na)

EXAMPLE 46

FR140105 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 1-(O^4-octyl-N,N-dimethyl-L-tyrosyl)-1H-benzotriazole-3-oxide according to a similar manner to that of Example 12.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (CD_3OD, δ): 0.91 (3H, t, J=6.8 Hz), 1.06 (3H, d, J=6.8 Hz), 1.12 (3H, d, J=6.1 Hz), 1.33 (10H, m), 1.74 (2H, m), 1.98 (3H, m), 2.40 (6H, s), 2.3–2.6 (3H, m), 2.8 (2H, m), 2.9–3.1 (1H, m), 3.3–3.5 (2H, m), 3.6–4.7 (16H, m), 5.06 (1H, d, J=3.8 Hz), 5.33 (1H, d, J=3 Hz), 6.77 (2H, d, J=8.6 Hz), 6.86 (1H, d, J=8.3 Hz), 7.03 (1H, dd, J=8.3 Hz and 2 Hz), 7.07 (2H, d, J=8.6 Hz), 7.31 (1H, d, J=2 Hz)

EXAMPLE 47

FR141564 substance was obtained by reacting FR133303 substance with 4-octyloxyphenylsulfonyl chloride according to a similar manner to that of Example 6.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (DMSO-d_6+D_2O, δ): 0.87 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.8 Hz), 1.04 (3H, d, J=5.7 Hz), 1.1–1.5 (10H, m), 1.6–2.1 (5H, m), 2.45 (3H, m), 2.5–2.7 (1H, m), 3.19 (1H, m), 3.7–4.5 (16H, m), 4.80 (1H, d, J=3 Hz), 4.88 (1H, d, J=4 Hz), 5.08 (1H, d, J=3 Hz), 6.74 (1H, d, J=8.2 Hz), 6.82 (1H, d, J=8.2 Hz), 6.84 (2H, d, J=8.7 Hz), 7.07 (1H, s), 7.51 (2H, d, J=8.7 Hz)

FAB-MS e/z=1249 (M+Na)

EXAMPLE 48

FR143170 substance was obtained by reacting FR133303 substance with 6-octyloxy-2-naphthylsulfonyl chloride according to a similar manner to that of Example 6.

IR (Nujol): 3300, 1620 cm^{-1}

NMR (CD_3OD, δ): 0.29 (3H, d, J=6.0 Hz), 0.91 (3H, t, J=6.7 Hz), 1.07 (3H, d, J=6.9 Hz), 1.25–1.6 (10H, m), 1.7–2.2 (5H, m), 2.2–2.6 (4H, m), 3.37 (1H, m), 3.55–4.65 (17H, m), 4.97 (1H, m), 5.54 (1H, m), 6.84 (1H, d, J=8.3 Hz), 7.01 (1H, dd, J=8.4 Hz and 2 Hz), 7.15–7.3 (3H, m), 7.75–8.0 (3H, m), 8.35 (1H, s)

FAB-MS e/z=1299 (M+Na)

EXAMPLE 49

To a solution of FR138364 substance (SEQ ID NO: 1) obtained in Example 5 (0.24 g) in acetonitrile (5 ml) was added p-toluenesulfonic acid (0.132 g) and stirred for 8 hours at room temperature. The reaction mixture was added to water and the aqueous layer was adjusted to pH 4.5 with saturated sodium bicarbonate aqueous solution. The aqueous solution was subjected to column chromatography on Diaion HP-20 and eluted with 80% aqueous methanol. The fractions containing the object compound were combined and evaporated under reduced pressure to remove methanol. The residue was

lyophilized to give FR138912 substance (SEQ ID NO: 1) (0.15 g).

IR (Nujol): 3300, 1620 cm^{-1}

FAB-MS e/z=1272 (M+K)

EXAMPLE 50

The mixture of FR138728 substance (SEQ ID NO: 1) obtained in Example 8 (0.15 g) and 1-octyl-1,4-dihydropyridine-4-thione (0.031 g) in N,N-dimethylformamide was stirred for 1.5 hours under ice-cooling. The reaction mixture was pulverized with diethyl ether (50 ml). The precipitate was filtrated and dried over phosphorus pentoxide under reduced pressure. The powder was added to water (300 ml) and adjusted to pH 4.5. The aqueous solution was subjected to column chromatography on Diaion HP-20 (50 ml) and eluted with 80% aqueous methanol. The fractions containing the object compound were combined and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give FR138960 substance (SEQ ID NO: 1) (0.15 g).

IR (Nujol): 3300, 1620 cm^{-1}

FAB-MS e/z=1222 (Free M+Na)

The following compounds (Examples 51 to 53) were obtained according to a similar manner to that of Example 3.

EXAMPLE 51

FR138727 substance (SEQ ID NO: 1)

NMR (CD_3OD, δ): 0.90 (3H, t, J=6.8 Hz), 1.05 (3H, d, J=6.8 Hz), 1.17-1.33 (13H, m), 1.6-1.8 (2H, m), 1.9-2.1 (3H, m), 2.50 (1H, m), 2.75 (1H, dd, J=16 Hz and 4 Hz), 3.40 (1H, m), 3.7-3.8 (1H, m), 3.98 (2H, t, J=6.2 Hz), 3.9-4.2 (5H, m), 4.3-4.5 (5H, m), 4.5-4.7 (3H, m), 4.97 (1H, d, J=3 Hz), 5.06 (1H, s), 5.20 (1H, d, J=3 Hz), 5.40 (1H, d, J=3 Hz), 6.85 (1H, d, J=8.3 Hz), 6.95 (2H, d,, J=8.5 Hz), 7.02 (1H, d, J=8.3 Hz), 7.30 (1H, d, J=8.5 Hz), 7.44 (1H, s)

EXAMPLE 52

FR138912 substance

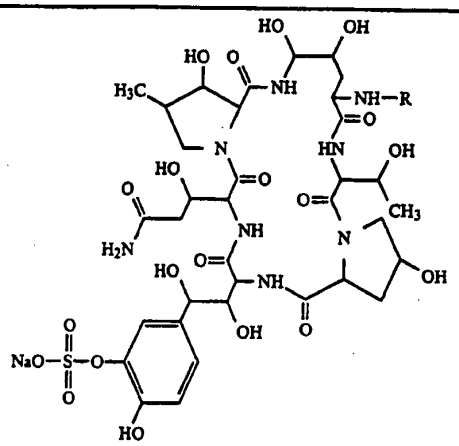
IR (Nujol): 3300, 1620 cm^{-1}

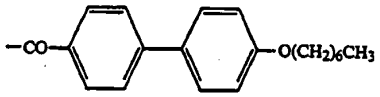
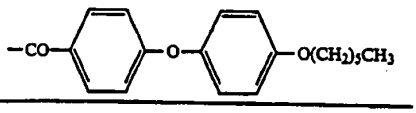
EXAMPLE 53

FR138960 substance

IR (Nujol): 3300, 1620 cm^{-1}

In the following, the structures of the compounds of Example 54 and 55 are shown (SEQ ID NO: 1).



Example No.	Compound No.	R
54	FR144274	
55	FR144271	

The following compounds (Examples 54 and 55) were obtained according to a similar manner to that of Example 3.

EXAMPLE 54

FR144274

IR (Nujol): 3300, 1620 cm^{-1}

Anal. Calcd. for $C_{55}H_{73}N_8SO_{22}Na\ 6H_2O$ C: 48.53, H: 6.29, N: 8.23, S: 2.35 Found C: 48.36, H: 6.34, N: 8.15, S: 2.30

FAB-MS e/z 1275 (M+Na)

EXAMPLE 55

FR144271

Anal. Calcd. for $C_{54}H_{71}N_8SO_{23}Na\ 6H_2O$ C: 47.57, H: 6.14, N: 8.22, S: 2.35 Found C: 47.58, H: 6.05, N: 8.18, S: 2.27

FAB-MS e/z=1277 (M+Na)

-continued

(1) GENERAL INFORMATION:

(i i i) NUMBER OF SEQUENCES: 1

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular

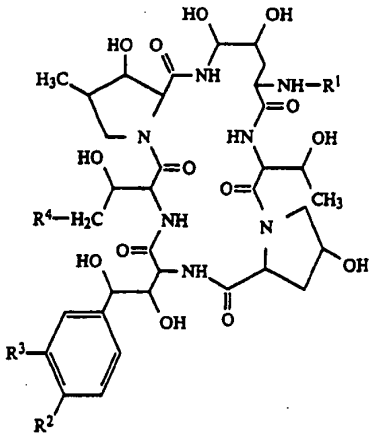
(i i) MOLECULE TYPE: protein

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Xaa Thr Xaa Xaa Xaa Xaa
1 5

What we claim is:

1. A polypeptide compound having antimicrobial activity of the following formula:



wherein

R^1 is a hydrogen or acyl group,

R^2 is hydroxy or acyloxy,

R^3 is hydroxysulfonyloxy, and

R^4 is hydrogen or carbamoyl,

with proviso that

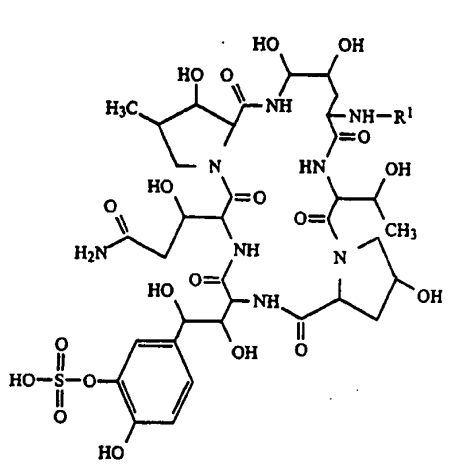
R^1 is not palmitoyl, when R^2 is hydroxy,

R^3 is hydroxysulfonyloxy and

R^4 is carbamoyl,

and a salt thereof.

2. A polypeptide compound of claim 1, which is shown by the following formula (SEQ ID NO: 1):



wherein R^1 is as defined above.

3. A compound of claim 2, wherein

R^1 is lower alkanoyl which may have one or more suitable substituent(s); higher alkanoyl, lower alkenoyl which may have one or more suitable substituent(s); higher alkenoyl; lower alkoxycarbonyl; higher alkoxycarbonyl; aryloxycarbonyl; arylglyoxyloyl; ar(lower)alkoxycarbonyl which may have one or more suitable substituent(s); lower alkylsulfonyl; arylsulfonyl which may have one or more suitable substituent(s); ar(lower)alkylsulfonyl; or aroyl which may have one or more suitable substituent(s).

4. A compound of claim 3, wherein

R^1 is lower alkanoyl; halo(lower)alkanoyl; ar(lower-)alkanoyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of hydroxy, lower alkoxy, higher alkoxy, aryl, amino, protected amino, di(lower)alkylamino, lower alkoxyimino and ar(lower)alkoxyimino which may have 1 to 3 higher alkoxy; heterocyclicthio(lower-)alkanoyl which may have 1 to 3 higher alkyl; heterocyclic(lower)alkanoyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkoxyimino, higher alkyl, amino and protected amino; ar(lower)alkoxyimino(lower)alkanoyl which may have 1 to 3 higher alkoxy; higher alkanoyl; ar(lower)alkenoyl which may have 1 to 3 higher alkoxy; higher alkenoyl; lower alkoxycarbonyl; higher alkoxycarbonyl;

aryloxycarbonyl; arylsulfonyl which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkyl and higher alkoxy; or aroyl which may have 1 to 5 suitable substituent(s) selected from the group consisting of halogen, lower alkyl, higher alkyl, carboxy, lower alkoxy which may have 1 to 10 halogen, lower alkoxy(lower)alkoxy, ar(lower)alkoxy, higher alkoxy which may have 1 to 17 halogen, higher alkenyloxy, aryl which may have 1 to 3 higher alkoxy and aryloxy which may have 1 to 3 lower alkoxy or higher alkoxy.

5. A compound of claim 4, wherein

R^1 is lower alkanoyl; halo(lower)alkanoyl; phenyl(lower)alkanoyl or naphthyl(lower)alkanoyl, each of which may have 1 to 3 suitable substituent(s) selected from the group consisting of hydroxy, lower alkoxy, higher alkoxy, phenyl, amino, lower alkoxycarbonylamino, di(lower)alkylamino, lower alkoxyimino and phenyl(lower)alkoxyimino which may have 1 to 3 higher alkoxy;

pyridylthio(lower)alkanoyl which may have 1 to 3 higher alkyl; imidazolyl(lower)alkanoyl or thiazolyl(lower)alkanoyl, each of which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkoxyimino, higher alkyl, amino and lower alkoxycarbonylamino;

phenyl(lower)alkoxyimino(lower)alkanoyl which may have 1 to 3 higher alkoxy; higher alkanoyl;

phenyl(lower)alkenoyl which may have 1 to 3 higher alkoxy; higher alkenoyl; lower alkoxycarbonyl, higher alkoxycarbonyl; phenoxycarbonyl; phenylsulfonyl or naphthylsulfonyl, each of which may have 1 to 3 suitable substituent(s) selected from the group consisting of lower alkyl and higher alkoxy; or, benzoyl, naphthoyl or anthrylcarbonyl, each of which may have 1 to 5 suitable substituent(s) selected from the group consisting of halogen, lower alkyl, higher alkyl, carboxy, lower alkoxy, which may have 6 to 10 halogen, lower alkoxy(lower)alkoxy, phenyl(lower)alkoxy, higher alkoxy which may have 12 to 17 halogen, higher alkenyloxy, phenyl which may have 1 to 3 higher alkoxy, and phenoxy which may have 1 to 3 lower alkoxy or higher alkoxy.

6. A compound of claim 5, wherein

R^1 is phenyl(lower)alkenoyl which may have 1 to 3 higher alkoxy; or benzoyl, naphthoyl or anthrylcarbonyl, each of which may have 1 to 5 suitable substituent(s) selected from the group consisting of halogen, lower alkyl, higher alkyl, carboxy, lower alkoxy which may have 6 to 10 halogen, lower alkoxy(lower)alkoxy, phenyl(lower)alkoxy, higher alkoxy which may have 12 to 17 halogen, higher alkenyloxy, phenyl which may have 1 to 3 higher alkoxy, and phenoxy which may have 1 to 3 lower alkoxy or higher alkoxy.

7. A compound of claim 6, wherein R^1 is phenyl(lower)alkenoyl which may have higher alkoxy; or benzoyl or naphthoyl, each of which may have higher alkoxy, higher alkenyloxy, or phenyl which may have higher alkoxy.

8. A compound of claim 7, wherein R^1 is benzoyl which has higher alkoxy.

9. A compound of claim 8, wherein R^1 is 4-octyloxybenzoyl.

10. A compound of Claim 7, wherein R^1 is phenyl(lower)alkenoyl which has higher alkoxy; or naphthoyl which was higher alkoxy or higher alkenyloxy.

11. A pharmaceutical composition having antimicrobial activity which comprises an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or excipient.

* * * * *

THN
6-8-98

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/809,723	05/21/97	OHRI	18-971-0-PCT

08/809,723

18-971-0 PCT

HM11/0605

OBLON SPIVAK MCCLELLAND
MAIER AND NEUSTADT
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON VA 22202

EXAMINER
MARSHALL, C

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 06/05/98

RD 9-5-98

NA 10-5-98 (1st)

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT P.C.

PTO-90C (Rev. 2/95)
*U.S. GPO: 1997-417-381/62715

2 - Mail Copy

Office Action Summary

Application No.	Applicant(s)
08/809723	Ohki et al
Examiner	**Group Art Unit**
Marshall	1654

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-16 and 19 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-16 and 19 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Claims 1-16 and 19 are pending in the case, and claims 17-18 have been cancel.

The rejection of claims 1-16 and 19 under 103(a) as being unpatentable over Toshiro et al (EPA0462531) or Toshiro et al (Us Patent 5, 376634) has been maintained as set forth in the office action mailed August 28, 1997 on pages 2-3 . Additionally, the rejection of claims 1-16 and 19 under the judicially created doctrine of obviousness-typed double patenting has been maintained.

Applicant's arguments filed March 2, 1998 have been fully considered but they are not persuasive.

Applicants agree with the examiner that the compounds of instant invention falls within the scope of the invention as taught by Toshiro et al. However, applicants' argue that the examiner provides no reason as to why one of skill in the art would be motivated from the teaching of the reference, to pick the specific acyl group of the instant invention.

Although the patent of Toshiro et al teaches R1 is acyl, Toshiro et al also define acyl groups as being lower alkanoyl, e.g. formyl , acetyl , propionyl, butyl... which may be substituted....(see Toshiro et al, col. 6, lines 30-68), , of which the preferred acyl is lower alkanoyl, including heterocyclic lower alkanoyl (see col.8, lines 14-68). These compounds read essentially on the compounds of applicants(see spec. 2-20) Therefore the compounds of the instant invention largely overlap the compounds of the reference, and one of ordinary skill in the art at the time that the invention was made would have been motivated to preferentially select the desired acyl group to obtain compounds of the instant invention that possess anitmicrobial

activity, especially anti fungal activity. Applicants' situation is not an In re Baird situation. In in re Baird, one would have to pick and choose from various radicals to come up with the claimed invention. In this invention, their is a large overlap in the compounds.

The Declaration submitted by applicants has been carefully considered, however; the small number of peptides tested is not commensurate in scope with the protection sought.Therefore the rejections are maintained. However, the specific compounds tested and showed unexpected results are allowable if presented.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Marshall whose telephone number is (703) 308-1030.

sgm
June 4, 1998

C Tsang

CECILIA J. TSANG
SUPERVISORY PATENT EXAMINER
GROUP 1800

DOCKET NO: 18-971-0 PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	:	
HIDENORI OHKI, ET AL.	:	GROUP ART UNIT: 1654
SERIAL NO: 08/809,723	:	EXAMINER: MARSHALL, S.
FILED: MAY 21, 1997	:	

FOR: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

AMENDMENT PURSUANT TO 37 C.F.R.§1.116

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

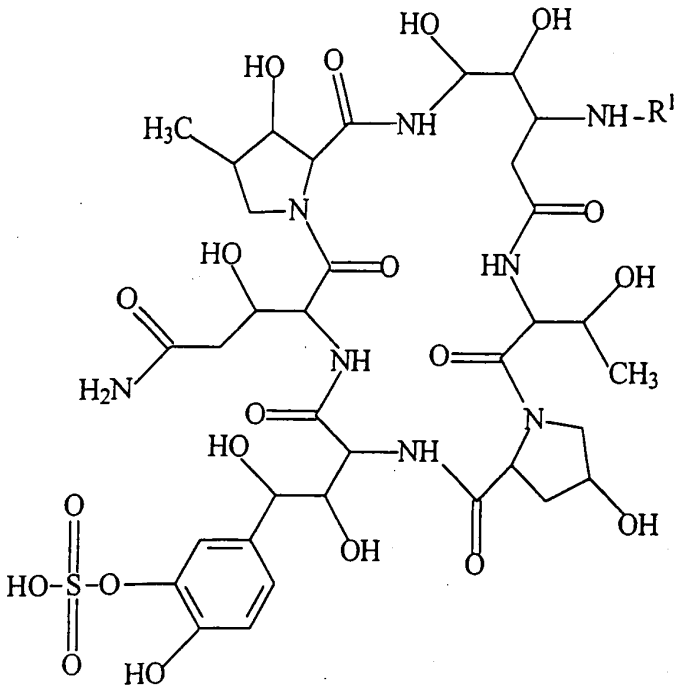
Responsive to the outstanding Office Action issued June 5, 1998, entry of the following amendments and remarks is respectfully requested. The amendment does not raise any new issues and serves to place the application in better form for appeal by reducing or simplifying the issues.

IN THE CLAIMS:

Please cancel Claims 1-16 and 19.

Please add the following new Claims:

--20. A polypeptide compound of the following general formula [I]:



[I]

wherein R^1 is selected from the group consisting of:

naphthyl (lower) alkenoyl which may have one or more higher alkoxy;

(C_2-C_6) alkanoyl substituted with naphthyl having higher alkoxy;

ar (C_2-C_6) alkanoyl substituted with aryl having one or more suitable substituent(s), wherein ar (C_2-C_6)-alkanoyl may have one or more suitable substituent(s);

aroyl substituted with a heterocyclic group which may have one or more suitable substituent(s), wherein aroyl may have one or more suitable substituent(s); and

a pharmaceutically acceptable salt thereof.

21. A compound of Claim 20, wherein R^1 is selected from the group consisting of:

naphthyl (lower) alkenoyl which may have 1 to 3 higher alkoxy;

ar (C_2-C_6) alkanoyl substituted with aryl having 1 to 3 substituent(s) selected from the

group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy (lower) alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy (lower) alkoxy, and oxo, wherein ar (C_2-C_6)-alkanoyl may have hydroxy, oxo, protected amino or amino; and

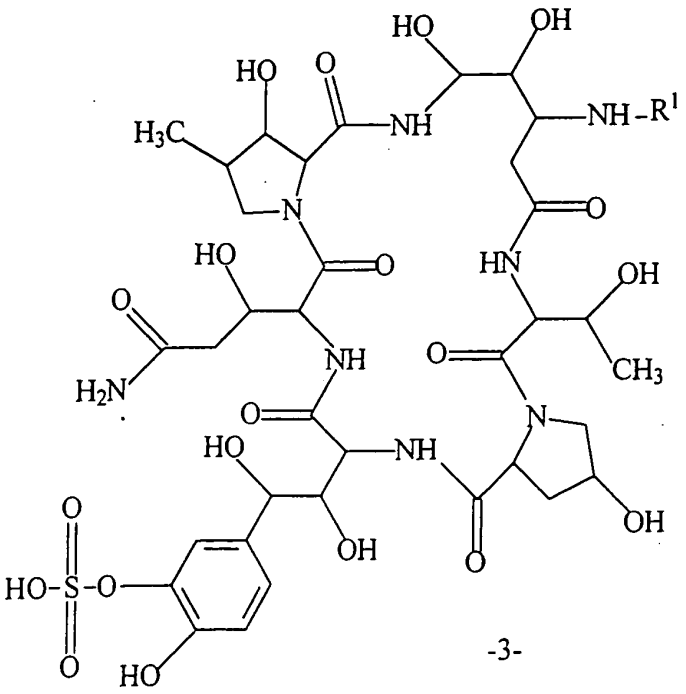
(C_2-C_6) alkanoyl substituted with naphthyl having higher alkoxy.

22. A compound of Claim 21, wherein R^1 is selected from the group consisting of: naphthyl (lower) alkenoyl which may have 1 to 3 higher alkoxy;

phenyl (C_2-C_6) alkanoyl substituted with phenyl which has 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, and phenyl having lower alkoxy (lower) alkyl, wherein phenyl (C_2-C_6) alkanoyl may have hydroxy, oxo, protected amino or amino; and

(C_2-C_6) alkanoyl substituted with naphthyl having higher alkoxy.

23. A polypeptide having the following general formula [I]:



[I]

wherein R^1 is aroyl substituted with a heterocyclic group which may have one or more suitable substituent(s), wherein aroyl may have one or more suitable substituent(s).

24. A compound of Claim 23, wherein R^1 is aroyl substituted with a heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy (lower) alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy (higher) alkoxy, phenyl having higher alkenyloxy, a heterocyclic group substituted with phenyl having lower alkoxy, a heterocyclic group, cyclo (lower) alkyl having phenyl, phenyl having cyclo (lower) alkyl, phenyl substituted with a heterocyclic group having lower alkyl and oxo, cyclo (lower) alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, and phenyl having a heterocyclic group and oxo, and wherein aroyl may also be substituted with halogen.

25. A compound of Claim 24, wherein R^1 is selected from the group consisting of:

benzoyl substituted with a saturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy (higher) alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, piperidyl, cyclo (lower) alkyl having phenyl, phenyl having cyclo (lower) alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl, wherein benzoyl may also be substituted with halogen;

benzoyl substituted with an unsaturated 5-membered heteromonocyclic group

containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy (higher) alkoxy, and phenyl substituted with phenyl having lower alkoxy;

benzoyl substituted with a 5 or 6-membered heteromonocyclic group containing 1 or 2 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl and phenyl having lower alkoxy; and

benzoyl substituted with a 5-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and 1 to 2 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo (lower) alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo (lower) alkyl, phenyl having piperidine, and phenyl having lower alkoxy (higher) alkoxy.

26. The compound of Claim 23, wherein R^1 is selected from the group consisting of:

benzoyl substituted with piperazinyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy (higher) alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, cyclo (lower) alkyl having phenyl, phenyl having cyclo (lower) alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl, and wherein benzoyl may also be substituted with halogen;

benzoyl substituted with isoxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy (higher) alkoxy, and phenyl substituted with phenyl

having lower alkoxy;

benzoyl substituted with thiadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo (lower) alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo (lower) alkyl, phenyl having piperidyl, and phenyl having lower alkoxy (higher) alkoxy; and

benzoyl substituted with oxadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy (higher) alkoxy, higher alkyl and phenyl substituted with phenyl having lower alkoxy.

27. A compound of Claim 26, wherein R^1 is selected from the group consisting of:

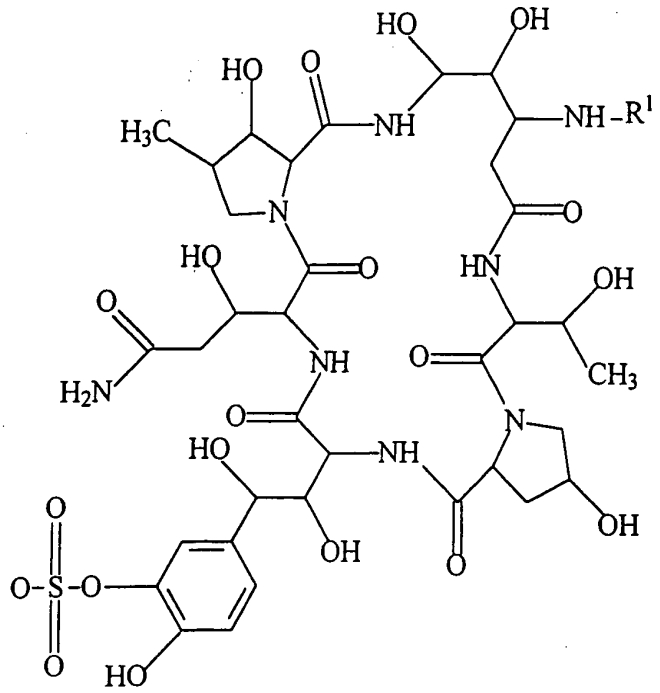
benzoyl substituted with piperazinyl which may have phenyl having lower alkoxy;

benzoyl substituted with isoxazolyl which may have phenyl having lower alkoxy;

benzoyl substituted with thiadiazolyl which may have phenyl having lower alkoxy (higher) alkoxy; and

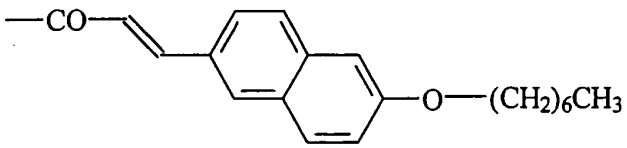
benzoyl substituted with oxadiazolyl which may have phenyl having lower alkoxy.

28. A polypeptide compound of the following general formula [I]:



[I]

wherein R^1 is selected from the group consisting of:



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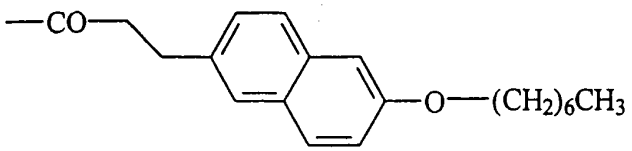

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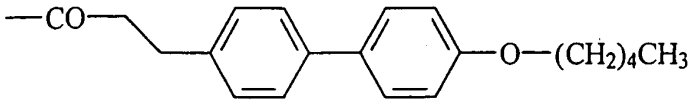

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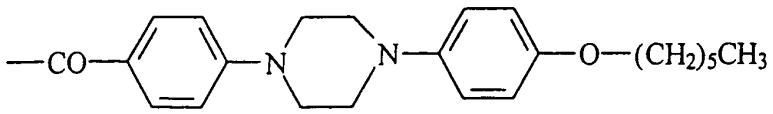
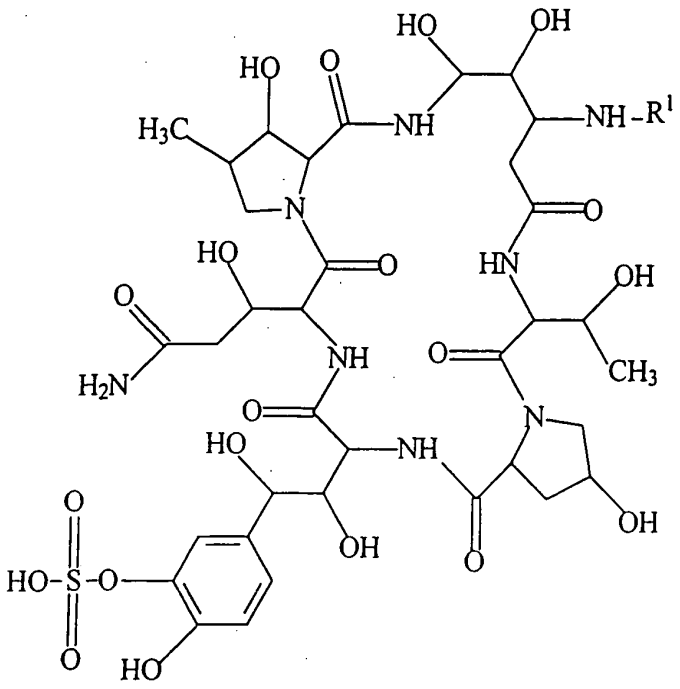


and a pharmaceutically acceptable salt thereof.

29. A process for the preparation of a polypeptide compound of the formula [I]:



[I]

wherein R^1 is selected from the group consisting of:

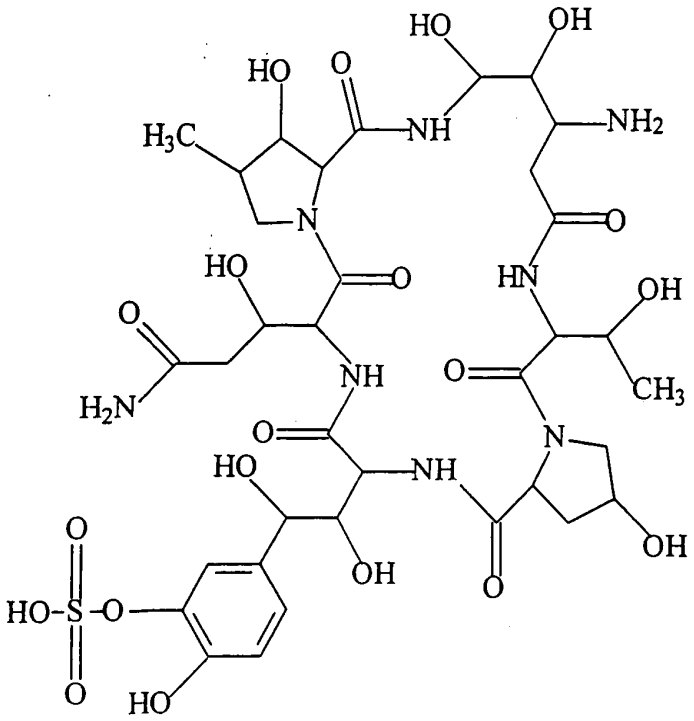
(C_2-C_6) alkanoyl substituted with naphthyl having higher alkoxy;

ar (C_2-C_6) alkanoyl substituted with aryl having one or more suitable substituent(s), wherein ar (C_2-C_6) alkanoyl may have one or more suitable substituent(s);

aroyl substituted with a heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s); and a pharmaceutically acceptable salt thereof,

which comprises

1) reacting a compound of the formula [II]:



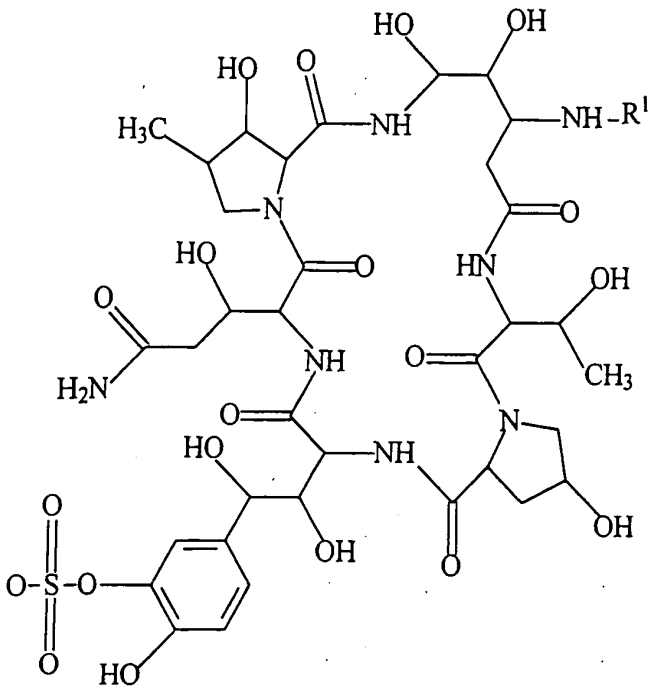
[II]

or its reactive derivative at the amino group or a salt thereof, with a compound of the formula [III]:

R^1 - OH [III]

wherein R^1 is defined above,

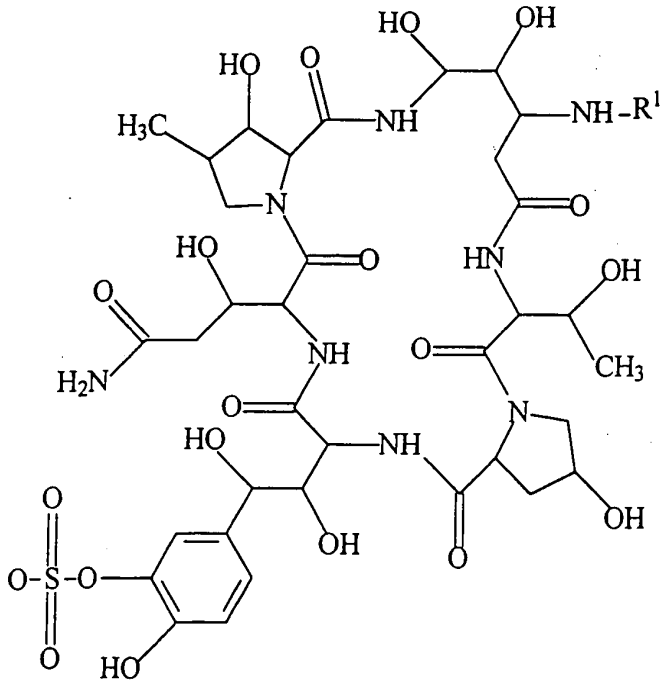
or its reactive derivative at the carboxy group or a salt thereof, to give a compound [I] of the formula:



[I]

wherein R^1 is defined above, or a salt thereof.

30. A process for the preparation of a polypeptide compound of the formula [I]:



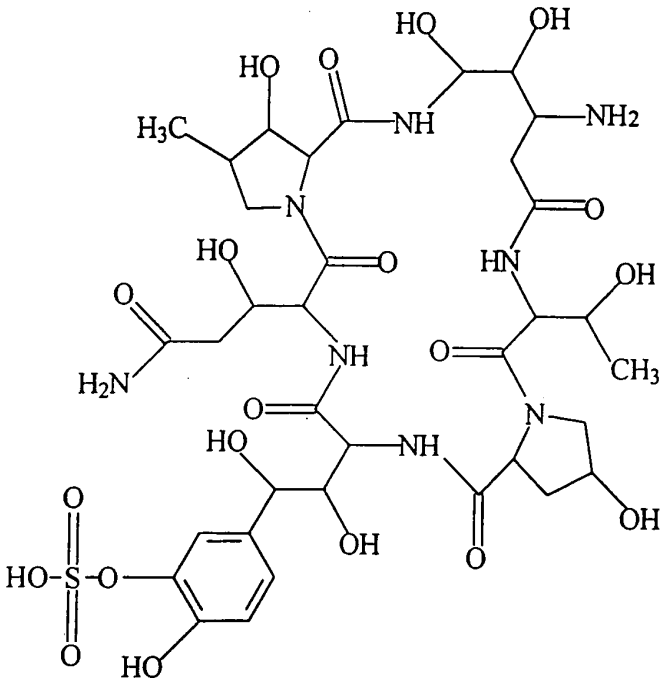
[I]

wherein R^1 is aroyl substituted with a heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s) or

a pharmaceutically acceptable salt thereof,

which comprises

1) reacting a compound of the formula [II]:



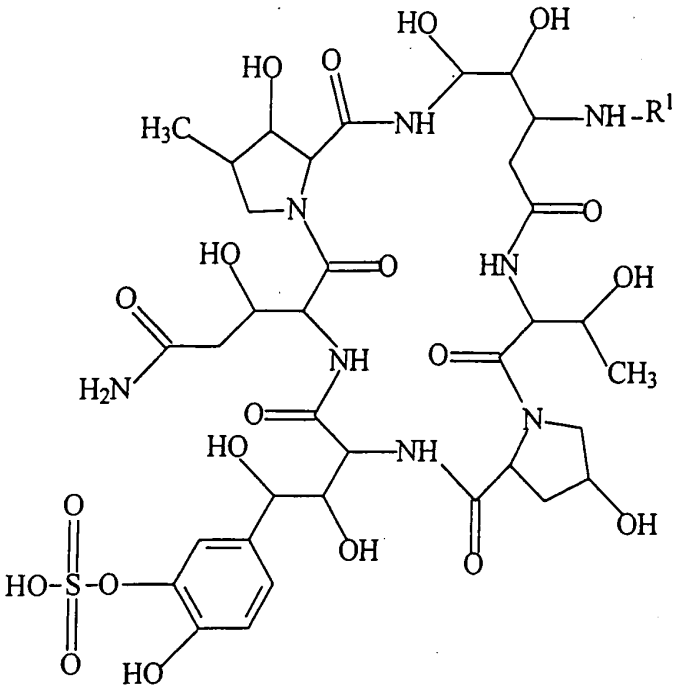
[II]

or its reactive derivative at the amino group or a salt thereof, with a compound of the formula [III]:

$$R^1 - OH \qquad [III]$$

wherein R^1 is defined above,

or its reactive derivative at the carboxy group or a salt thereof, to give a compound [I] of the formula:



[I]

wherein R^1 is defined above, or a salt thereof.

31. A pharmaceutical composition which comprises, as an active ingredient, a compound of Claim 20 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers of excipients.

32. A pharmaceutical composition which comprises, as an active ingredient, a compound of Claim 23 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers of excipients.

33. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which comprises administering a compound of Claim 20 or a pharmaceutically acceptable salt thereof to a human being or an animal.

34. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which comprises administering a compound

of Claim 23 or a pharmaceutically acceptable salt thereof to a human being or an animal.

35. A pharmaceutical composition which comprises, as an active ingredient, a compound of Claim 28 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers of excipients.

36. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which comprises administering a compound of Claim 28 or a pharmaceutically acceptable salt thereof to a human being or an animal.--

SUPPORT FOR THE AMENDMENTS

New Claims 20-36 are supported by original Claims 1-16 and 19. Support for Claim 28 can be found on page 17 of the specification as originally filed. No new matter has been added. Claims 20-36 remain active in the case.

REMARKS

Applicants appreciate the interview granted undersigned counsel in the above-captioned application, wherein it was argued that new Claim 20 is commensurate in scope with the showing of superior results using the claimed compounds, presented in the Declaration under 37 C.F.R. §1.132 filed March 2, 1998, since the compounds encompassed by Claim 20 are homologs of the specific compounds tested. The Examiner agreed to give the arguments presented in a request for reconsideration careful consideration. Applicants appreciate the Examiner's acknowledgment that the specific compounds tested showed unexpected results and would be allowable if presented in independent form.

The present invention relates to cyclic hexapeptide compounds having antimicrobial activity in humans and animals, a process for preparing the compounds, a pharmaceutical

composition containing the compound and a method of using the compounds for the prophylactic or therapeutic treatment of infectious diseases.

The rejection of Claims 1-16 and 19 under 103(a) over Toshiro et al. (EP A 0462531) or Toshiro et al. (US Patent 5,376,634) is respectfully traversed.

Since the disclosure of US 5,376,634 appears to be identical to EP 0 462 531, the following discussion applies to both references.

Toshiro et al. does not disclose Applicant's cyclic hexapeptide. The R_1 substituent on the compounds of Toshiro et al. may be either hydrogen or acyl, whereas in the presently claimed compounds it must be acyl. Toshiro et al. disclose that suitable acyl groups are those listed at column 6, line 30 through column 8, line 5. This encompasses hundreds of compounds. However, none of the acyl groups described is an aroyl substituted with a heterocyclic group, as recited in Claim 23 of the instant application. The only description of R_1 being an aroyl group is at column 7, line 44, but there is no description of the aroyl group being substituted with a heterocyclic group. Nor are there any examples in Toshiro et al. of compounds wherein the R_1 is aroyl substitued with a heterocyclic group. Therefore it is respectfully submitted that independent Claims 23 and 30, wherein R_1 is aroyl substituted with a heterocyclic group and Claims 24-27, 32 and 34, dependent therefrom, are all patentable over Toshiro et al.

Applicants have shown, via the Declaration filed March 2, 1998, the superiority of the presently claimed compounds compared to two of the preferred compounds in Toshiro et al. The Examiner agreed that a claim to those specific compounds would be allowable if presented. Therefore, Applicants have presented Claim 28, which is drawn to examples 16, 20, 21 and 23 from the specification which were shown in the Declaration to have superior

antifungal properties compared to two of the preferred compounds in Toshiro et al. Therefore, Claim 28 and Claims 35 and 36, dependent therefrom are submitted to be patentable over Toshiro et al.

Claim 20 has been limited to four choices for R^1 which are submitted to be representative of the compounds of Examples 16, 20, 21 and 23, shown to have superior antifungal activity. Specifically, R^1 may be: naphthyl(lower)alkenoyl which may have one or more higher alkoxy, which is representative of the compound of Example 21 in which R^1 is naphthyl-C_2-alkenoyl having a C_7-alkoxy group; (C_2-C_6) alkanoyl substituted with naphthyl having higher alkoxy, which is representative of the compound of Example 20 in which R^1 is C_2 alkanoyl substituted with naphthyl having a C_7 alkoxy group; ar(C_2-C_6)alkanoyl substituted with aryl having one or more suitable substituents, which is representative of the compound of Example 16 in which R^1 is phenyl-C_2-alkanoyl substituted with phenyl having C_7 alkoxy; and aroyl substituted with a heterocyclic group which may have one or more suitable substituents, which is representative of the compound of Example 23 in which R^1 is phenoyl substituted with piperazinyl which is substituted with phenyl having a C_6 alkoxy group. The above-described R^1 groups should be considered to be representative of the specific compounds shown in the Declaration since they are homologs, i.e., a family of related compounds, the composition of which varies from member to member by a CH_2 group. Chemists knowing the properties of one member would in general know what to expect in adjacent members. Objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support. By the same token, Applicant is not required to test each and every species within the scope of the claims. Rather, patentability is established by a showing of unexpected superiority for representative

λ_{max}^{KBr}: 3350, 2920, 2840, 1660, 1625, 1530, 1510, 1435, 1270, 1240, 1070, 1045, 800, 755, 710 cm^{-1}

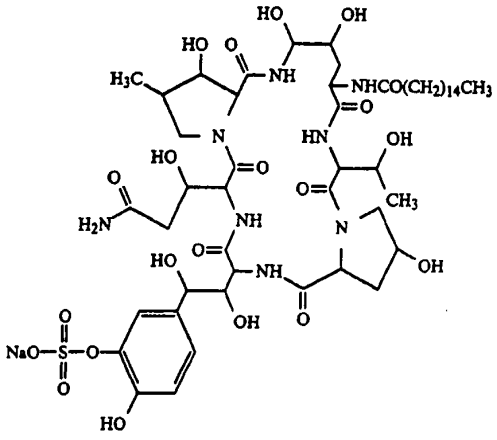
^1H Nuclear magnetic resonance spectrum:

(CD_3OD, 400 MHz)

δ: 7.30 (1H, d, J=2 Hz), 7.03 (1H, dd, J=8 and 2 Hz), 6.85 (1H, d, J=8 Hz), 5.23 (1H, d, J=3 Hz),

5.06 (1H, d, J=4 Hz), 4.93 (1H, d, J=3 Hz), 4.59–4.51 (3H, m), 4.47–4.35 (5H, m), 4.29 (1H, dd, J=6 and 2 Hz), 4.17 (1H, m), 4.07 (1H, m), 3.95–3.89 (2H, m), 3.76 (1H, broad d, J=11 Hz), 3.36 (1H, m), 2.75 (1H, dd, J=16 and 4 Hz), 2.50 (1H, m), 2.47 (1H, dd, J=16 and 9 Hz), 2.38 (1H, m), 2.21 (2H, m), 2.03–1.93 (3H, m), 1.57 (2H, m), 1.45–1.20 (24H, m), 1.19 (3H, d, J=6 Hz), 1.08 (3H, d, J=6 Hz), 0.90 (3H, t, J=7 Hz)

From the analysis of the above physical and chemical properties, and the result of the further investigation of identification of chemical structure, the chemical structure of the FR901379 substance (SEQ ID NO: 1) has been identified and assigned as follows.



EXAMPLE 1

N-acyl group of FR901379 substance (SEQ ID NO: 1) was eliminated by the reaction with an enzyme. In the following, this elimination process is explained in detail.

(1) Fermentation of Actinoplanes utahensis

The enzyme which is useful for eliminating N-acyl group of FR901379 substance (SEQ ID NO: 1) is produced by certain microorganisms of the Actinoplanaceae, preferably the microorganism Actinoplanes utahensis IFO-13244.

A stock culture of Actinoplanes utahensis IFO-13244 is prepared and maintained on agar slant. A loopful of the slant culture was inoculated into a seed medium consisted of starch 1%, sucrose 1%, glucose 1%, cotton seed flour 1%, peptone 0.5%, soy bean meal 0.5% and $CaCO_3$ 0.1%. The inoculated vegetative medium was incubated in a 225-ml wide mouth Erlenmeyer flask at 30° C. for about 72 hours on a rotary shaker.

This incubated vegetative medium was used directly to inoculate into a production medium consisted of sucrose 2%, peanut powder 1%, K_2HPO_4 0.12% KH_2PO_4 0.05% and $MgSO_4$ $7H_2O$ 0.025%. The inoculated production medium was allowed to ferment in a 30-liter jar fermentor at a temperature of 30° C. for about 80 hours. The fermentation medium was stirred with conventional agitators at 250 rpm and aerated at 20 liters per minute. The vegetative mycelium was collected from the fermented broth by filtration and once washed with water. The washed mycelium was directly used to eliminate N-acyl group of FR901379 substance (SEQ ID NO: 1) as an enzyme source.

(2) Elimination Condition

FR901379 substance was dissolved in 0.25M phosphate buffer (pH 6.5) at a concentration of 0.9 mg/ml. To a 36-liter of the solution was added a 2 kg wet weight of washed mycelium of Actinoplanes utahensis IFO-13244. The elimination reaction was carried out at 37° C. under for 23 hours. Reduction of FR901379 substance (SEQ ID NO: 1) and increase of the deacylated FR901379 substance (SEQ ID NO: 1) (hereinafter referred to as FR133303 substance) were measured using a HPLC equipped with a reverse phase column. From a 30 g of FR901379 substance (SEQ ID NO: 1), a 22.2 g of FR133303 substance was formed in the reaction mixture.

(3) Isolation of FR133303 Substance (SEQ ID NO: 1)

The reaction mixture described above was filtered with a filter aid. The mycelial cake was discarded. The filtrate thus obtained was passed through a column of activated carbon (2 L). The column was washed with 6 L of water and eluted with 12 L of 50% aqueous acetone. The eluate was evaporated in vacuo to remove acetone and then passed through a column (4 L) of YMC GEL ODS-AM 120-S50 (Yamamura Chemical Labs). The column was washed with water and eluted with 2% aqueous acetonitrile containing 50 mM NaH_2PO_4. Elution was monitored by analytical HPLC, using a column of LiChrospher 100 RP-18 (Cica-MERCK) and a solvent system of 3% aqueous acetonitrile containing 0.5% $NH_4H_2PO_4$ at a flow rate of 1 ml/min, detecting the FR133303 substance with a UV monitor at 210 nm. The fractions containing the FR133303 substance were combined and passed through a column of activated carbon (400 ml). The column was washed with water and eluted with 50% aqueous acetone. The eluate was concentrated in vacuo to remove acetone and lyophilized to give 16.4 g of FR133303 substance (SEQ ID NO: 1) as a white powder.

FR133303 substance (SEQ ID NO: 1) has following physico-chemical properties:

Appearance:

white powder

Melting point:

150°–160° C.(dec.)

Specific rotation:

$[\alpha]_D^{24}$ −31.17° (C: 1.0, H_2O)

Molecular formula:

$C_{35}H_{51}N_8SO_{20}Na$

Elemental Analysis:

Calcd: for $C_{35}H_{51}N_8SO_{20}Na$ C 43.84, H 5.36, N 11.69, S 3.34 (%) Found: C 41.14, H 5.74, N 10.88, S 3.10 (%)

Solubility:

soluble: water

slightly soluble: methanol

insoluble: n-hexane

Color reaction:

positive: iodine vapor reaction, cerium sulfate reaction, Ninhydrin reaction

negative: Molish reaction

Thin layer chromatography (TLC):

Stationary phase	Developing solvent	Rf value
silica gel*	n-butanol:acetic acid	0.15

-continued

Thin layer chromatography (TLC):		
Stationary phase	Developing solvent	Rf value
	water (3:1:2)	

Silica Gel 60 (made by E. Merck)

Ultraviolet absorption spectrum:

λ_{max}^{H2O} ($E_{1\,cm}^{1\%}$): 201(340), 273(18), 224(sh), 281(sh) nm

$\lambda_{max}^{H2O+0.01M\text{-}NaOH}$ ($E_{1\,cm}^{1\%}$): 207(414), 243(122), 292(34)

Infrared absorption spectrum:

ν_{max}^{KBr}: 3350, 2920, 1660, 1625, 1515, 1440, 1270, 1080, 1045, 800, 755, 715 cm^{-1}

^1H Nuclear magnetic resonance spectrum:

(D_2O, 400 MHz)

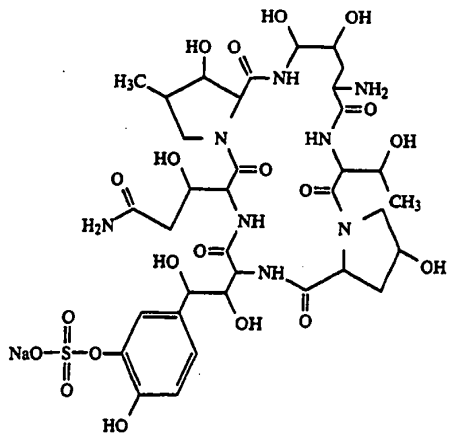
δ: 7.31 (1H, d, J=2 Hz), 7.12 (1H, dd, J=2 Hz and 8 Hz), 7.06 (1H, d, J=8 Hz), 5.40 (1H, d, J=3 Hz), 5.04 (1H, d, J=3.5 Hz), 4.94 (1H, d, J=6 Hz), 4.73–4.55 (3H, m), 4.51–4.38 (4H, m), 4.31–4.23 (3H, m), 4.11–4.06 (2H, m), 3.94–3.89 (2H, m), 3.41 (1H, m), 2.60–2.34 (5H, m), 2.14 (1H, m), 2.03 (1H, m), 1.28 (3H, d, J=6 Hz), 1.01 (3H, d, J=6.5 Hz)

^{13}C Nuclear magnetic resonance spectrum:

(D_2O, 100 MHz)

δ: 178.3 (s), 175.9 (s), 174.3 (s), 174.2 (s), 174.0 (s), 171.8 (s), 171.3 (s), 150.9 (s), 141.5 (s), 134.4 (s), 128.2 (d), 124.5 (d), 120.3 (d), 78.1 (d), 77.0 (d), 76.9 (d], 76.6 (d), 72.9 [d), 72.8 (d), 71.2 (d), 69.3 (d), 69.2 (d), 63.7 (d), 60.1 (d), 58.3 (t), 58.0 (d), 56.9 (d), 55.3 (d), 54.7 (t), 41.8 (t), 39.7 (d), 39.5 (t), 33.5 (t), 21.4 (g), 13.3 (g)

The chemical structure of FR133303 substance (SEQ ID NO: 1) has been identified and assigned as follows.



EXAMPLE 2

(1) A solution of 4-hydroxybenzoic acid (19.2 g) in 10% NaOH (120 ml) was dropwise added to 480 ml of dimethyl sulfoxide over 30 minutes during which the temperature in reaction mixture was controlled between 30° and 40° C. After adding, the solution was cooled to 17°–20° C. 1-Bromooctane (28.95 g) was dropwise added to the solution over 30 minutes and the reaction mixture was vigorously stirred for 4 hours at room temperature. The reaction mixture was poured into ice water (1200 ml) and acidified with 40 ml of conc. hydrochloric acid. After vigorously stirring for another 1 hour, the resulting solid was removed by filtration and dissolved in 60 ml of acetonitrile. The solution was refluxed over 30 minutes and was allowed to stand overnight at room temperature to yield 4-octyloxybenzoic acid (13.8 g) as a crystal (MP 96° C., Anal Calcd. for $C_{15}H_{22}O_3$: C 71.97, H 8.86, Found: C 71.30, H 8.89).

To a solution of 4-octyloxybenzoic acid (13.8 g) in diethyl ether (552 ml) were added 2,4,5-trichlorophenol (10.87 g) and N,N'-dicyclohexylcarbodiimide (11.37 g). The solution was stirred under a nitrogen atmosphere for 18 hours at room temperature. The precipitate was removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in petroleum ether and was allowed to stand on ice-water. The resulting crystals (15.2 g) were filtered and dissolved in warm n-hexane (150 ml). After standing overnight at room temperature, the resulting crystal was removed by filtration. The filtrate was concentrated to an oil which was purified by a column chromatography over silica gel using a mixture of ethyl acetate and n-hexane to give 2,4,5-trichlorophenyl 4-octyloxybenzoate (7.58 g) (MP 53° C., Anal Calcd. for $C_{21}H_{23}O_3Cl_3$: Cl 24.75, Found: Cl 24.05).

(2) To a solution of FR133303 substance (SEQ ID NO: 1) (2.04 g) in N,N-dimethylformamide (60 ml) were added 2,4,5-trichlorophenyl 4-octyloxybenzoate (2.04 g) and 4-dimethylaminopyridine (0.283 g). The solution was stirred under a nitrogen atmosphere at room temperature for 15 hours. 4-Dimethylaminopyridine (0.20 g) was added to the solution and mixture was stirred for another 24 hours. The reaction mixture was poured into water (600 ml) and the pH was adjusted to 6.0. The mixture was washed twice with an equal volume of ethyl acetate and concentrated to 30 ml. The concentrate was applied on a column (150 ml) of DEAE-Toyopearl (Cl type, manufactured by Tosoh). The column was washed with 50% aqueous methanol and developed with 50% aqueous methanol containing 1M sodium chloride aqueous solution. The elution of product was assessed by the same HPLC system as described in Example 1(3) except that the concentration of acetonitrile in solvent was 40%. The fractions containing the object compound were pooled and evaporated in vacuo to remove methanol. The solution was absorbed on a column (1 L) of YMC GEL ODS-AM 120-S50 in order to remove salt. The column was washed with water and eluted with 30% aqueous acetonitrile. The eluate was evaporated in vacuo to remove acetonitrile and lyophylized to give the object compound (hereinafter referred to as FR131535 substance (SEQ ID NO: 1)) (1.4 g) as a white powder.

FR131535 substance has following physico-chemical properties:

Appearance:

white powder

Melting point:

170°–189° C. (dec.)

Specific rotation:

$[\alpha]_D^{20}$ −14.4° (C: 10, H_2O)

Molecular formula:

$C_{50}H_{71}N_8SO_{22}Na$

Elemental Analysis:

Calcd: for $C_{50}H_{71}N_8SO_{22}Na.6H_2O$ C 46.22, H 6.44, N 8.62, S 2.46, Na 1.77 (%) Found: C 46.80, H 6.13, N 8.78, S 1.96, Na 1.81 (%)

Solubility:

soluble: methanol, water

slightly soluble: acetone

insoluble: n-hexane

Color reaction:

positive: iodine vapor reaction, cerium sulfate reaction

Thin layer chromatography (TLC):

Stationary phase	Developing solvent	Rf value
silica gel*	n-butanol:acetic acid: water (6:1:1)	0.21

*Silica Gel 60 (made by E. Merck)

Infrared absorption spectrum:

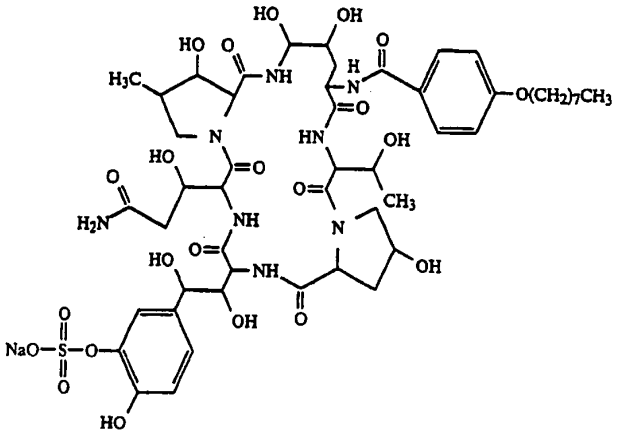
ν_{max}^{KBr}: 3330, 2900, 2850, 1620, 1500, 1430, 1270, 1250, 1170, 1110, 1080, 1040, 960, 940, 880, 840, 800, 750, 710 cm^{-1}

^1H Nuclear magnetic resonance spectrum:

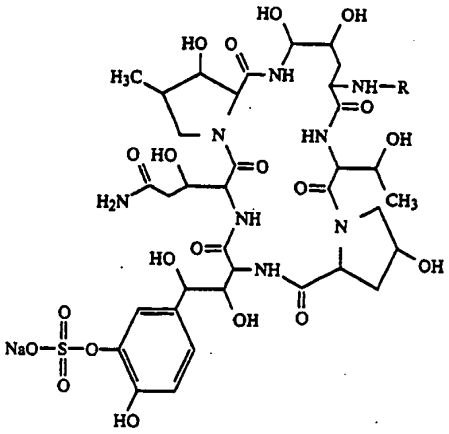
(CD_3OD, 200 MHz)

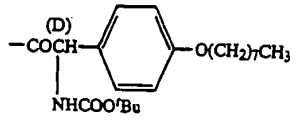
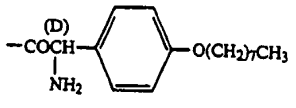
δ: 7.78 (2H, d, J=8 Hz), 7.31 (1H, d, J=2 Hz), 7.03 (1H, dd, J=8 Hz and 8 Hz), 6.96 (2H, d, J=8 Hz), 6.87 (1H, d, J=8 Hz), 5.33 (1H, d, J=3 Hz), 5.08 (1H, d, J=4 Hz), 4.99 (1H, d, J=3 Hz), 4.80–3.20 (17H, m), 2.83 (1H, m), 2.65–2.30 (4H, m), 2.22–1.90 (2H, m), 1.79 (2H, m), 1.56–1.25 (10H, m), 1.19 (3H, d, J=6 Hz), 1.06 (3H, d, J=6.5 Hz), 0.90 (3H, t, J=6.5 Hz)

The chemical structure of FR131535 substance (SEQ ID NO: 1) has been identified and assigned as follows.

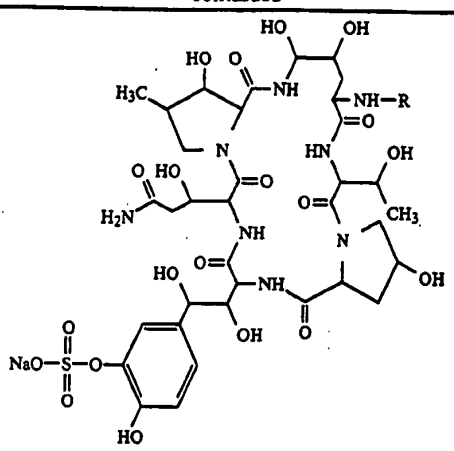


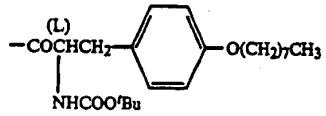
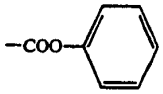
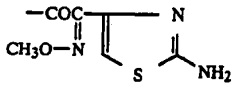
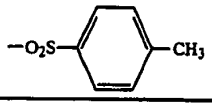
In the following, the structures of the compounds Examples 3 to 11 are shown (SEQ ID NO: 1).



Example No.	Compound No.	R
3	FR138260	
4	FR138727	

-continued



Example No.	Compound No.	R
5	FR138364	
6	FR138261	$-COO^tBu$
7	FR138363	$-COCH_3$
8	FR138728	$-COCH_2Br$
9	FR138538	
10	FR138539	
11	FR138365	

EXAMPLE 3

To a solution of FR133303 substance (SEQ ID NO: 1) (1 g) and N-(t-butoxycarbonyl)-D-2-(p-octyloxyphenyl)glycine succinimido ester (0.596 g) in N,N-dimethylformamide (3 ml) was added 4-dimethylaminopyridine (0.165 g). The mixture was stirred for 12 hours at room temperature. The reaction mixture was added to water (30 ml) and then adjusted to pH 6. The aqueous solution was washed with ethyl acetate, and subjected to ion exchange chromatography on DEAE-Toyopearl ($Cl^{\ominus}$) (60 ml) and eluted with 50% methanol in 1M aqueous solution of sodium chloride. The fractions containing the object compound were combined and evaporated under reduced pressure to remove methanol. The aqueous solution was adjusted to pH 4.5 with 1N hydrochloric acid and subjected to column chromatography on Diaion HP-20 (Trademark, Manufactured by Mitsubishi Chemical Industries) (130 ml) and eluted with 80% aqueous methanol. The fractions containing the object compound were combined and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give object acylated compound (hereinafter referred to as FR138260 substance (SEQ ID NO: 1)) (0.77 g).

IR (Nujol): 3300, 1660, 1500, 1240, 1045, 800, 720 cm^{-1}

NMR (CD_3OD, δ): 0.92 (3H, t, J=6.8 Hz), 1.05 (3H, d, J=6.8 Hz), 1.17–1.33 (13H, m), 1.43 (9H, s), 1.6–1.8 (2H, m), 1.9–2.1 (3H, m), 2.50 (3H, m), 2.75 (1H, dd, J=16 Hz and 4 Hz), 3.35 (1H, m), 3.7–3.8 (1H, m), 3.93 (2H, t, J=6.2 Hz), 3.9–4.2 (5H, m), 4.3–4.5 (5H, m), 4.5–4.7 (3H, m), 4.97 (1H, d, J=3 Hz), 5.05 (1H, d, J=4 Hz), 5.11 (1H, s), 5.30 (1H, d, J=3 Hz), 6.85 (1H, d, J=8.3 Hz), 6.86 (2H, d, J=8.6 Hz), 7.02 (1H, d, J=8.3 Hz), 7.26 (2H, d, J=8.6 Hz), 7.31 (1H, s)

FAB-MS: e/z=1343 (M+Na)

EXAMPLE 4

FR138260 substance (SEQ ID NO: 1) obtained in Example 3 (0.25 g) was added to trifluoroacetic acid (1.25 ml) and stirred for 10 minutes. The reaction mixture was added to water (30 ml) and then adjusted to pH 4.5 with saturated aqueous solution of sodium bicarbonate. The aqueous solution was subjected to column chromatography on Diaion HP-20 (100 ml) and eluted with 80% aqueous methanol. The fractions containing

the object compound were combined and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give the object compound (hereinafter referred to as FR138727 substance) (SEQ ID NO: 1) (15 mg).

NMR (CD_3OD, δ): 0.90 (3H, t, J=6.8 Hz), 1.05 (3H, d, J=6.8 Hz), 1.17–1.33 (13H, m), 1.6–1.8 (2H, m), 1.9–2.1 (3H, m), 2.50 (1H, m), 2.75 (1H, dd, J=16 Hz and 4 Hz), 3.40 (1/4, m), 3.7–3.8 (1H, m), 3.98 (2H, t, J=6.2 Hz), 3.9–4.2 (5H, m), 4.3–4.5 (5H, m), 4.5–4.7 (3H, m), 4.97 (1H, d, J=3 Hz), 5.06 (1H, s), 5.20 (1H, d, J=3 Hz), 5.40 (1H, d, J=3 Hz), 6.85 (1H, d, J=8.3 Hz), 6.95 (2H, d,

J=8.5 Hz), 7.02 (1H, d, J=8.3 Hz), 7.30 (1H, d, J=8.5 Hz), 7.44 (1H, s)

FAB-MS: e/z=12.59 (M+K)

EXAMPLE 5

FR138364 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with O^4-octyl-N-(t-butoxycarbonyl)-L-tyrosine succinimido ester according to a similar manner to that of Example 3.

IR (Nujol): 3300, 1660, 1620, 1240, 1050 cm^{-1}

NMR (CD_3OD, δ): 0.904 (3H, t, J=6.8 Hz), 1.06 (3H, d, J=6.8 Hz), 1.17 (3H, d, J=6.7 Hz), 1.20–1.30 (10H, m), 1.35 (9H, s), 1.74 (2B, quintet, J=6.5 Hz), 1.9–2.1 (3H, m), 2.45 (3H, m), 2.76 (1H, dd, J=16 Hz and 4 Hz), 3.0–3.1 (2B, m), 3.37 (1H, m), 3.77 (1H, d, J=11 Hz), 3.92 (2H, t, J=6.8 Hz), 3.9–4.2 (7B, m), 4.3–4.5 (5H, m), 4.5–4.6 (3H, m), 4.94 (1H, d, J=3 Hz), 5.05 (1H, d, J=3.8 Hz), 5.31 (1H, d, J=3 Hz), 6.79 (2H, d, J=8.5 Hz), 6.85 (1H, d, J=S.3Hz), 7.03 (1H, dd, J=8.3 Hz and 2 Hz), 7.12 (2H, d, J=8.5 Hz), 7.31 (1H, d, J=2 Hz)

FAB-MS: e/z=1357 (M+Na)

EXAMPLE 6

A solution of FR133303 substance (SEQ ID NO: 1) (0.5 g) in a mixture of water (5 ml) and tetrahydrofuran (5 ml) was adjusted to pH 7 with saturated aqueous solution of sodium bicarbonate and N,N-di-t-butylcarbonate (0.114 g) was added thereto at room temperature. The mixture was stirred for 5 hours at room temperature maintaining pH 7 with saturated aqueous solution of sodium bicarbonate. The reaction mixture was added to water and adjusted to pH6. The aqueous solution was washed with ethyl acetate, and subjected to ion exchange chromatography on DEAE-Toyopearl (Cl^-) (30 ml) and eluted with 50% methanol in 1M aqueous solution of sodium chloride. The fractions containing the object compound were combined and evaporated under reduced pressure to remove methanol. The aqueous solution was adjusted to pH 4.5 with 1N hydrochloric acid and subjected to column chromatography on Diaion HP-20 (100 ml) and eluted with 80% aqueous methanol. The fractions containing the object compound were combined and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give the object acylated compound (hereinafter referred to as FR138261 substance) (SEQ ID NO: 1) (0.145 g).

IR (Nujol): 3300, 1660, 1620, 1240, 1050 cm^{-1}

NMR (CD_3OD, δ): 1.06 (3H, d, J=6.8 Hz), 1.18 (3H, d, J=6.0 Hz), 1.40 (9H, s), 1.9–2.1 (3H, m), 2.44 (3H, m), 2.82 (1/{, dd, J=16 Hz and 4 Hz), 3.37 (1H, m), 3.75 (1H, d, J=11Hz), 3.89–4 (2H, m), 4.10 (1H, m), 4.15 (1H, m), 4.29 (1H, dd, J=6 Hz and 2 Hz), 4.36–4.45 (5H, m), 4.5–4.6 (3H, m), 4.97 (1H, d, J=3 Hz), 5.06 (1H, dd, J=8.2 Hz and 4 Hz), 5.33 (1H, d, J=3 Hz), 6.85 (1H, d, J=8.3 Hz), 7.03 (1H, dd, J=8.3 Hz and 2 Hz), 7.30 (1H, d, J=2 Hz), 7.50 (1H, d, J=8.2 Hz)

FAB-MS: e/z=1081 (M+Na)

EXAMPLE 7

FR138363 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with acetyl chloride according to a similar manner to that of Example 6.

IR (Nujol): 3300, 1620, 1250, 1040 cm^{-1}

NMR (CD_3OD, δ): 1.06 (3H, d, J=6.8 Hz), 1.20 (3H, d, J=6 Hz), 1.78–2.05 (3H, m), 1.96 (3H, s), 2.21–2.54 (3H, m), 2.95 (1H, m), 3.35–3.42 (1H, m), 3.58–4.42 (11H, m), 4.50–5.05 (5H, m), 5.23 (1H, m), 6.88 (1H, d, J=8.3 Hz), 7.05 (1H, dd, J=8.3 Hz and 2 Hz), 7.35 (1H, d, J=2 Hz)

FAB-MS: 1023 (M+Na)

EXAMPLE 8

FR138728 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 2-bromoacetyl chloride according to a similar manner to that of Example 6.

IR (Nujol): 3300, 1660, 1620, 1500, 1220, 1040 cm^{-1}

NMR (CD_3OD, δ): 1.06 (3H, d, J=6.9 Hz), 1.17 (3H, d, J=6.1 Hz), 1.9–2.1 (3H, m), 2.50 (3H, m), 2.80 (1H, dd, J=16 Hz and 4 Hz), 3.37 (1H, m), 3.6–4.0 (5H, m), 4.09 (1H, m), 4.16 (1H, m), 4.29 (1H, dd, J=6 Hz and 2 Hz), 4.36–4.45 (5H, m), 4.5–4.7 (3H, m), 4.97 (1H, d, J=3 Hz), 5.04 (1H, dd, J=8.6 Hz and 4 Hz), 5.25 (1H, d, J=3.1 Hz), 6.85 (1H, d, J=8.3 Hz), 7.03 (1H, dd, J=8.3 Hz and 2.1 Hz), 7.31 (1H, d, J=2 Hz), 7.52 (1H, d, J=8.6 Hz)

FAB-MS: e/z=1103 (M+Na)

EXAMPLE 9

FR138538 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with benzoyl chloride according to a similar manner to that of Example 6.

IR (Nujol): 3300, 1640, 1240 cm^{-1}

NMR (CD_3OD, δ): 1.05 (3H, d, J=6.8 Hz), 1.18 (3H, d, J=6 Hz), 1.89–2.12 (3H, m), 2.31–2.53 (3H, m), 2.75 (1H, dd, J=12 Hz and 4 Hz), 3.38 (1H, m), 3.76 (1H, d, J=11Hz), 3.87–3.98 (1H, m), 4.02–4.18 (2H, m), 4.22–4.32 (4H, m), 4.37–4.40 (3H, m), 4.49–4.62 (3H, m), 4.98 (1H, m), 5.02 (1H, m), 5.37 (1H, d, J=3 Hz), 6.85 (1H, d, J=8.3 Hz), 7.04 (1H, dd, J=8.3 Hz and 2 Hz), 7.11–7.50 (6H, m)

FAB-MS: e/z=1101 (M+Na)

EXAMPLE 10

FR138539 substance (SEQ ID NO: 1) was obtained by reacting FR133303 substance (SEQ ID NO: 1) with 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid according to a similar manner to that of Example 6.

IR (Nujol): 3300, 1650, 1620, 1520, 1260, 1040 cm^{-1}

NMR (CD_3OD, δ): 1.05 (3H, d, J=6.8 Hz), 1.21 (3H, d, J=5.9 Hz), 1.89–2.21 (3H, m), 2–29–2.61 (3H, m), 2.78–2.89 (1H, m), 3.32–3.42 (1H, m), 3.76–3.82 (1H, m), 3–91–4.01 (2H, m), 3.95 (3H, s), 4.13 (1H, m), 4.16 (1H, m), 4.24–4.27 (1H, m), 4.32–4.43 (5H, m), 4.46–4.62 (3H, m), 4.97–4.99 (1H, m), 5.08 (1H, m), 5.41 (1H, m), 6.79 (1H, s), 6.86 (1H, d, J=8.1 Hz), 7.04 (1H, dd, J=8.1 Hz and 2 Hz), 7.31 (1H, d, J=2 Hz), 7.51 (1H, d, J=7 Hz)

FAB-MS: e/z=1143 (M+)

EXAMPLE 11

FR138365 substance (SEQ ID NO: 1) obtained by reacting FR133303 substance (SEQ ID NO: 1) with tosyl chloride according to a similar manner to that of Example 6.

IR (Nujol): 3300, 1650, 1620, 1260, 1060 cm^{-1}

NMR (CD_3OD, δ): 0.75 (3H, d, J=6.8 Hz), 1.07 (3H, d, J=6.0 Hz), 1.61–1.79 (1H, m), 1.91–2.05 (3H, m), 2.30–2.59 (3H, m), 3.36 (1H, m), 3.68 (1H, d, J=11 Hz), 3.81–4.07 (4H, m), 4.22 (1H, m), 4.32–4.40 (5H, m), 4.42–4.60 (3H, m), 4.7 (1H, m), 5.0 (1H, m), 5.42 (1H, d, J=3 Hz), 6.85 (1H, d, J=8.3 Hz), 7.03 (1H, dd, J=8.3 Hz and 2 Hz), 7.29–7.33 (3H, m), 7.75 (1H, d, J=8.3 Hz)

FAB-MS: e/z=1135 (M+Na)

Preparation 11

To a solution of 6-hydroxy-2-naphthoic acid (1 g) in the mixture of 10% sodium hydroxide aqueous solution (4.25 ml) and dimethylsulfoxide (17 ml) was added octyl bromide (0.918 ml). The mixture was stirred for 6 hours at 60° C.

The reaction mixture was added to a mixture of water and ethyl acetate and adjusted to pH 3 with conc. hydrochloric acid. The organic layer was separated and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 6-octyloxy-2-naphthoic acid (0.91 g).

IR (Nujol): 1670, 1620, 1210 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.2–1.6 (10H, m), 1.78 (2H, m), 4.10 (2H, t, J=6.7 Hz), 7.19 (1H, dd, J=2.3 and 8.8 Hz), 7.36 (1H, d, J=2.3 Hz), 7.83 (1H, d, J=8.8 Hz), 7.97 (2H, d, J=8.8 Hz), 8.52 (1H, s)

Preparation 12

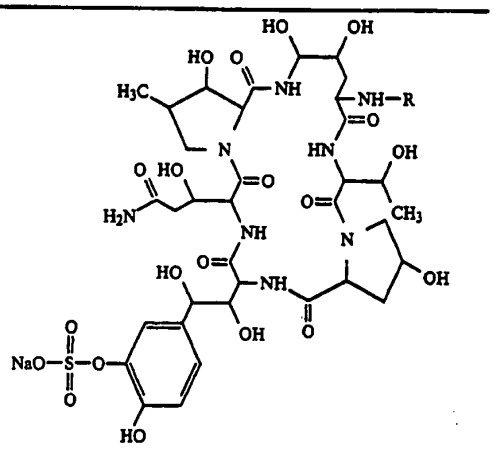
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.703 g) was added to a solution of 6-octyloxy-2-naphthoic acid (0.85 g) and 1-hydroxy-1H-benzotriazole (0.382 g) in ethyl acetate (26 ml). The mixture was stirred for two hours at room temperature.

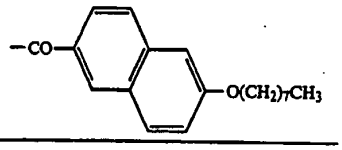
The reaction mixture was added to water and the separated organic layer was washed with water and sodium chloride aqueous solution. Then the organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-(6-octyloxy-2-naphthoyl)-1H-benzotriazole-3-oxide (0.74 g).

IR (Nujol): 1770, 1740, 1620, 1190, 1020, 740 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.8 Hz), 1.2–1.6 (10H, m), 1.89 (2H, m), 4.14 (2H, t, J=6.8 Hz), 7.1–7.3 (2H, m), 7.4–7.6 (3H, m), 7.8–8.0 (2H, m), 8.1–8.2 (2H, m), 8.80 (1H, s)

In the following, the structure of the compound of Example 12 is shown.



Example No.	Compound No.	R
12	FR139687	

EXAMPLE 12

To a solution of FR133303 substance (0.5 g) and 1-(6-octyloxy-2-naphthoyl)-1H-benzotriazole-3-oxide (0.271 g) in N,N-dimethylformamide (1.5 ml) was added 4-dimethylaminopyridine (0.0828 g). The mixture was stirred for 12 hours at room temperature.

The reaction mixture was added to water and adjusted to pH 6. The aqueous solution was washed with ethyl acetate, and subjected to ion exchange chromatography on DEAE-Toyopearl (Cl^-) (30 ml) and eluted with 50% methanol in 1M sodium chloride solution. The fractions containing the object compound were combined and evaporated under reduced pressure to remove methanol. The aqueous solution was adjusted to pH 4.5 with 1N hydrochloric acid and subjected to column chromatography on Diaion HP-20 (65 ml) and eluted with 80% aqueous methanol. The fractions containing the object compound were combined and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give object acylated compound (hereinafter referred to as FR139687 substance) (0.214 g).

IR (Nujol): 3300, 1620, 1500 cm^{-1}

NMR (DMSO-d_6+D_2O, δ): 0.86 (3H, t, J=6.8 Hz), 0.97 (3H, d, J=6.8 Hz), 1.06 (3H, d, J=6.8 Hz), 1.2–1.5 (10H, m), 1.6–2.0 (5H, m), 2.2–2.5 (3H, m), 2.4–2.6 (1H, m), 3.18 (1H, m), 3.6–3.9 (1H, m), 4.0–4.6 (15H, m), 4.84 (1H, d, J=3 Hz), 4.90 (1H, d, J=3 Hz), 5.11 (1H, d, J=3 Hz), 6.76 (1H, d, J=8.3 Hz), 6.93 (1H, d, J=8.3 Hz), 7.13 (1H, s), 7.25 (1H, d, J=8.3 Hz), 7.39 (1H, s), 7.8–8.0 (3H, m), 8.44 (1H, s)

FAB-MS e/z=1264 (M+Na) The following compounds (Preparations 13 to 16) were obtained according to a similar manner to that of Preparation 5.

Preparation 13

N-(t-Butoxycarbonyl)-L-2-(2-naphthyl)glycine succinimido ester

IR (Nujol): 3350, 1800, 1770, 1730, 1680, 1500, 1200 cm^{-1}

Preparation 14

Succinimido 2-(4-biphenylyl)acetate

IR (Nujol): 1800, 1770, 1720, 1200 cm^{-1}

NMR (DMSO-d_6, δ): 2.82 (4H, s), 4.17 (2H, s), 7.30–7.50 (5H, m), 7.45 (2H, d, J=8.1 Hz), 7.67 (2H, d, J=8.1 Hz)

Preparation 15

Succinimido 4-t-butylbenzoate

IR (Nujol): 1760, 1730, 1200, 1070, 990 cm^{-1}

NMR (DMSO-d_6, δ): 1.33 (9H, s), 2.89 (4H, s), 7.68 (2H, d, J=8.5 Hz), 8.03 (2H, d, J=8.5 Hz)

Preparation 16

Succinimido 4-(4-phenylbutoxy)benzoate

IR (Nujol): 1730, 1600, 1240, 1170, 1070 cm^{-1}

NMR (DMSO-d_6, δ): 1.75 (4H, m), 2.65 (2H, m), 4.14 (2H, m), 7.15 (2H, d, J=8.9 Hz), 7.13–7.35 (5H, m), 8.03 (2H, d, J=8.9 Hz)

Preparation 17

To neat 3,7-dimethyloctanol (5 ml) was added phosphorus tribromide (1.01 ml). The mixture was stirred for 4 hours at 60° C. The reaction mixture was added to a mixture of water and n-hexane. The organic layer was separated and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 3,7-dimethyloctyl bromide (4.40 g).

IR (Neat): 2900, 1450 cm^{-1}

NMR ($CDCl_3$, δ): 0.87 (6H, d, J=6.6 Hz), 0.89 (3H, d, J=6.4 Hz), 1.1–1.3 (6H, m), 1.5–1.9 (4H, m), 3.3–3.5 (2H, m)

The following compounds (Preparations 18 to 23) were obtained according to a similar manner to that of Preparation 11.

Preparation 18

4-[4-(Octyloxy)phenoxy]benzoic acid

IR (Nujol): 1680, 1600, 1240, 840 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 1.1–1.6 (10H, m), 1.71 (2H, m), 3.96 (2H, t, J=6.4 Hz), 6.9–7.1 (6H, m), 7.92 (2H, d, J=8.7 Hz), 12.8 (1H, br s)

Preparation 19

6-(Butoxy)-2-naphthoic acid

IR (Nujol): 1660, 1610, 1205 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, t, J=7.29 Hz), 1.48 (2H, qt, J=7.29 Hz and 7 Hz), 1.78 (2H, tt, J=7 Hz and qt, J=7.29 Hz and 7 Hz), 1.78 (2H, tt, J=7Hz and 6.45 Hz), 4.12 (2H, t, J=6.45 Hz), 7.24 (1H, dd, J=9.0 Hz and 2.3 Hz), 7.40 (1H, d, J=2.3 Hz), 7.86 (1H, d, J=8.7 Hz), 7.94 (1H, d, J=8.7 Hz), 8.01 (1H, d, J=9.0 Hz), 8.52 (1H, s)

Preparation 20

6-Decyloxy-2-naphthoic acid

IR (Nujol): 1670, 1620, 1210 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 1.2–1.6 (14H, m), 1.78 (2H, m), 4.11 (2H, t, J=6.4 Hz), 7.23 (1H, dd, J=8.9 Hz and 2.4 Hz), 7.39 (1H, d, J=2.4 Hz), 7.86 (1H, d, J=8.7 Hz), 7.93 (1H, d, J=8.7 Hz), 8.01 (1H, d, J=8.9 Hz), 8.5 (1H, s)

Preparation 21

6-Hexyloxy-2-naphthoic acid

IR (Nujol): 1660, 1620, 1290, 1210 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.6 (6H, m), 1.78 (2H, quint, J=6.5 Hz), 4.11 (2H, t, J=6.5 Hz), 7.23 (1H, dd, J=9.0 Hz and 2.4 Hz), 7.39 (1H, d, J=2.4 Hz), 7.86 (1H, d, J=8.7 Hz), 7.94 (1H, d, J=8.7 Hz), 8.01 (1H, d, J=9.0 Hz), 8.52 (1H, s)

Preparation 22

6-Dodecyloxy-2-naphthoic acid

IR (Nujol): 1670, 1620, 1210 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 1.20–1.60 (18H, m), 1.78 (2H, m), 4.11 (2H, t, J=6.5 Hz), 7.22 (1H, dd, J=9.0 Hz and 2.4 Hz), 7.39 (1H, d, J=2.4 Hz), 7.85 (1H, d, J=8.7 Hz), 7.93 (1H, d, J=8.7 Hz), 8.00 (1H, d, J=9.0 Hz), 8.51 (1H, s), 12.90 (1H, s)

Preparation 23

6-(3,7-Dimethyloctyloxy)-2-naphthoic acid

IR (Nujol): 1660, 1610, 1290, 1210 cm^{-1}

NMR (DMSO-d_6, δ): 0.84 (6H, d, J=6.6 Hz), 0.94 (3H, d, J=6.1 Hz), 1.1–1.4 (6H, m), 1.4–1.9 (4H, m), 4.15 (2H, t, J=6.7 Hz), 7.22 (1H, dd, J=9.0 Hz and 2.4 Hz), 7.4i (1H, d, J=2.4 Hz), 7.86 (1H, d, J=8.6 Hz), 7.93 (1H, d, J=8.6 Hz), 8.01 (1H, d, J=9.0 Hz), 8.52 (1H, s)

The following compounds (Preparations 24 to 31) were obtained according to a similar manner to that of Preparation 12.

Preparation 24

1-[4-(4-Octyloxy)phenoxy]benzoyl-1H-benzotriazole-3-oxide

IR (Nujol): 1770, 1730, 1600, 1500, 1230, 980 cm^{-1}

Preparation 25

1-(6-Butoxy-2-naphthoyl)-1H-benzotriazole-3-oxide

IR (Nujol): 1760, 1610, 1260, 1180, 1020 cm^{-1}

Preparation 26

1-(6-Decyloxy-2-naphthoyl)-1H-benzotriazole-3-oxide

IR (Nujol): 1780, 1620, 1190, 1000 cm^{-1}

Preparation 27

1-(6-Hexyloxy-2-naphthoyl)-1H-benzotriazole-3-oxide

IR (Nujol): 1780, 1610, 1190 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.6 (6H, m), 1.79 (2H, m), 4.12 (2H, t, J=6.5 Hz), 7.24 (1H, dd, J=9.0 Hz and 2.4 Hz), 7.39 (1H, d, J=2.4 Hz), 7.41 (1H, t, J=8 Hz), 7.54 (1H, t, J=8 Hz), 7.72 (1H, d, J=8 Hz), 7.88 (1H, d, J=8.7 Hz), 7.90 (1H, d, J=8.7 Hz), 7.97 (1H, d, J=8 Hz), 8.02 (1H, d, J=9.0 Hz), 8.51 (1H, s)

Preparation 28

1-(6-Dodecyloxy-2-naphthoyl)-1H-benzotriazole-3-oxide

IR (Nujol): 1770, 1620, 1190, 1030, 730 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 1.2–1.3 (18H, m), 1.78 (2H, m), 4.11 (2H, t, J=6.5 Hz), 7.22 (1H, dd, J=9.0 Hz and 2.4 Hz), 7.39 (1H, d, J=2.4 Hz), 7.40 (1H, t, J=8 Hz), 7.55 (1H, t, J=8 Hz), 7.73 (1H, d, J=8 Hz), 7.85 (1H, d, J=8.7 Hz), 7.93 (1H, d, J=8.7 Hz), 7.99 (1H, d, J=8 Hz), 8.00 (1H, d, J=9.0 Hz), 8.51 (1H, s)

Preparation 29

1-[6-(3,7-Dimethyloctyloxy)-2-naphthoyl]-1H-benzotriazole-3-oxide

IR (Nujol): 1780, 1620, 1190 cm^{-1}

Preparation 30

1-[(2E,6E)-3,7,11-Trimethyl-2,6,10-dodecatrienoyl]-1H-benzotriazole-3-oxide

IR (Neat): 2900, 1780, 1620, 1420, 1070 cm^{-1}

Preparation 31

3,7-Dimethyl-6-octenyl bromide was obtained according to a similar manner to that of Preparation 17.

IR (Neat): 2900, 1440, 1380 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, d, J=6.3 Hz), 1.0–1.5 (2H, m), 1.57 (3H, s), 1.65 (3H, s), 1.7–2.1 (5H, m), 3.4-.3.7 (2H, m), 5.08 (1H, m)

Preparation 32

To a suspension of sodium hydride (2.04 g) in N,N-dimethylformamide (50 ml) was added 4-hydroxypyridine (5 g) at room temperature. Octyl bromide (9.08 ml) was added thereto. The mixture was stirred for 2 hours at 50° C. The reaction mixture was added to a mixture of brine (100 ml), trtrahydrofuran (100 ml) and ethyl acetate (100 ml). The organic layer was separated and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-octyl-4-pyridone (14.7 g).

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6 Hz), 1.1–1.4 (10H, m), 1.4–1.8 (2H, m), 3.81 (2H, t, J=7 Hz), 6.05 (2H, d, J=8 Hz), 7.63 (2H, d, J=8 Hz)

Preparation 33

To a solution of 1-octyl-4-pyridone (10.9 g) in pyridine (100 ml) was added phosphorous pentasulfide (8.65 g) at room temperature. The mixture was stirred for 3 hours at 80° C. The reaction mixture was added to a mixture of water (200 ml) and methylene chloride (200 ml). The organic layer was separated and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-octyl-1,4-dihydropyridine-4-thione (5.27 g).

IR (Neat): 2910, 2850, 1620, 1460, 1110 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6 Hz), 1.1–1.4 (10H, m), 1.5–1.9 (2H, m), 3.95 (2H, t, J=7 Hz), 7.13 (2H, d, J=7 Hz), 7.60 (2H, d, J=7 Hz)

The following compounds (Preparations 34 to 36) were obtained according to a similar manner to that of Preparation 1.

Preparation 34

Methyl 2-(4-hydroxyphenyl)-2-methoxyacetate

IR (Nujol): 3350, 1740, 1610, 1600, 1220, 1100 cm^{-1}

NMR (DMSO-d_6, δ): 3.23 (3H, s), 3.60 (3H, s), 4.73 (1H, s), 6.72 (2H, d, J=8.9 Hz), 7.15 (2H, d, J=8.9 Hz)

EI-MS (e/z)=196 (M^+)

Preparation 35

D-Tyrosine methyl ester hydrochloride

IR (Nujol): 3300, 1740, 1220 cm^{-1}

NMR (DMSO-d_6, δ): 3.02 (2H, m), 3.67 (3H, s), 4.16 (1H, t, J=6.7 Hz), 6.72 (2H, d, J=8.4 Hz), 7.01 (2H, d, J=8.4 Hz), 8.58 (2H, s), 9.47 (1H, s)

Preparation 36

Methyl (4-hydroxyphenyl)glyoxylate

IR (Nujol): 3380, 1730, 1700, 1600, 1580, 1220 cm^{-1}

NMR (DMSO-d_6, δ): 3.91 (3H, s), 6.94 (2H, d, J=8.8 Hz), 7.83 (2H, d, J=8.8 Hz), 10.9 (1H, s)

Preparation 37

N-(t-Butoxycarbonyl)-D-tyrosine methyl ester was obtained according to a similar manner to that of Preparation 2.

IR (Nujol): 3360, 1700, 1680, 1290, 1270, 1250 cm^{-1}

NMR (DMSO-d_6, δ): 1.33 (9H, s), 2.73 (2H, m), 3.59 (3H, s), 4.05 (1H, m), 6.65 (2H, d, J=8.4 Hz), 7.00 (2H, d, J=8.4 Hz), 7.23 (1H, d, J=7.9 Hz), 9.23 (1H, s)

Preparation 38

To a solution of L-tyrosine methyl ester hydrochloride (1 g) in water (1.5 ml) was added sodium bicarbonate (0.363 g) under ice-cooling and stirred for 10 minutes, and then acetonitrile (7 ml), 37% formaldehyde aqueous solution (0.637 ml) and sodium cyanoborohydride (0.182 g) was added thereto at −5° C. The mixture was stirred for 2 hours at −5° C. The resultant insoluble material was filtered off, and the filtrate was extracted with ethyl acetate. The organic layer was separated and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give N,N-dimethyl-L-tyrosine methyl ester (0.21 g).

IR (Nujol): 1730, 1260, 1010 cm^{-1}

NMR (DMSO-d_6, δ): 2.24 (6H, s), 2.72 (2H, m), 3.34 (1H, m), 3.53 (3H, s), 6.54 (2H, d, J=8.4 Hz), 6.97 (2H, d, J=8.4 Hz), 9.18 (1H, s)

The following compounds (Preparations 39 to 44) were obtained according to a similar manner to that of Preparation 3.

Preparation 39

Methyl 2-(4-octyloxyphenyl)acetate

IR (Neat): 2910, 2850, 1730, 1240 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.3 Hz), 1.2–1.5 (10H, m), 1.6–1.9 (2H, m), 3.58 (2H, s), 3.59 (3H, s), 3.92 (2H, t, J=6.4 Hz), 6.85 (2H, d, J=8.7 Hz), 7.15 (2H, d, J=8.7 Hz)

Preparation 40

Ethyl 3-(4-octyloxyphenyl)propionate

IR (Neat): 2920, 2850, 1730, 1240 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.15 (3H, t, J=7.1 Hz), 1.2–1–5 (10H, m), 1.6–1.8 (2H, m), 2.55 (2H, t, J=7.2 Hz), 2.77 (2H, t, J=7.2 Hz), 3.90 (2H, t, J=6.4 Hz), 4.03 (2H, q, J=7.1 Hz), 6.81 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.6 Hz)

Preparation 41

Methyl 2-(4-octyloxyphenyl)-2-methoxyacetate

IR (Neat): 2910, 2850, 1740, 1600, 1240, 1100 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 3.26 (3H, s), 3.62 (3H, s), 3.94 (2H, t, J=6.4 Hz), 4.83 (1H, s), 6.91 (2H, d, J=8.7 Hz), 7.27 (2H, d, J=8.7 Hz)

EI-MS (e/z)=308 (M^+)

Preparation 42

O^4-Octyl-N-(t-butoxycarbonyl)-D-tyrosine methyl ester

IR (Nujol): 3350, 1730, 1680, 1510, 1240, 1160 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.2–1.3 (10H, m), 1.68 (2H, m), 2.82 (2H, m), 3.60 (3H, s), 3.91 (2H, t, J=7.3 Hz), 4.08 (1H, m), 6.81 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=8.6 Hz), 7.25 (1H, d, J=8.0 Hz)

US005376634A

United States Patent [19]

Iwamoto et al.

[11] Patent Number: 5,376,634

[45] Date of Patent: Dec. 27, 1994

[54] POLYPEPTIDE COMPOUND AND A PROCESS FOR PREPARATION THEREOF

[75] Inventors: Toshiro Iwamoto, Tsukuba; Akihiko Fujie, Tsuchiura; Kumiko Nitta, Tsuchiura; Yasuhisa Tsurumi; Nobuharu Shigematsu, both of Tsukuba; Chiyoshi Kasahara, Ikeda; Motohiro Hino, Tsuchiura; Masakuni Okuhara, Tsukuba; Kazuo Sakane, Kawanishi; Kohji Kawabata, Kawanishi; Hidenori Ohki, Ikeda, all of Japan

[73] Assignee: Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan

[21] Appl. No.: 715,961

[22] Filed: Jun. 17, 1991

[30] Foreign Application Priority Data

Jun. 18, 1990 [GB] United Kingdom 9013558
Oct. 31, 1990 [GB] United Kingdom 9023666
Jan. 24, 1991 [GB] United Kingdom 9101552

[51] Int. Cl.[5] C07K 5/12; C07K 7/06; A61K 37/02

[52] U.S. Cl. 514/9; 514/11; 530/317

[58] Field of Search 530/317; 514/9, 11

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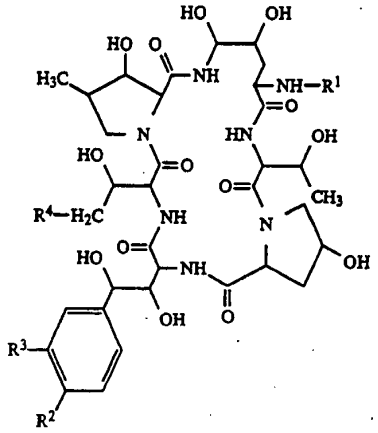
2066263 11/1980 United Kingdom .

Primary Examiner—Robert J. Hill, Jr.
Assistant Examiner—S. G. Marshall
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

A polypeptide compound having antimicrobial activity of the following general formula:



wherein R^1 is hydrogen or acyl group,
R^2 is hydroxy or acyloxy,
R^3 is hydroxysulfonyloxy, and
R^4 is hydrogen or carbamoyl,

with proviso that
R^1 is not palmitoyl, when R^2 is hydroxy,
R^3 is hydroxysulfonyloxy and
R^4 is carbamoyl,

and a pharmaceutically acceptable salt thereof.

11 Claims, No Drawings

POLYPEPTIDE COMPOUND AND A PROCESS FOR PREPARATION THEREOF

The present invention relates to new polypeptide compound and a pharmaceutically acceptable salt thereof.

More particularly, it relates to new polypeptide compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities (especially antifungal activities), to a process for preparation thereof, to pharmaceutical composition comprising the same, and to a method for treating or preventing infectious diseases in human being or animals.

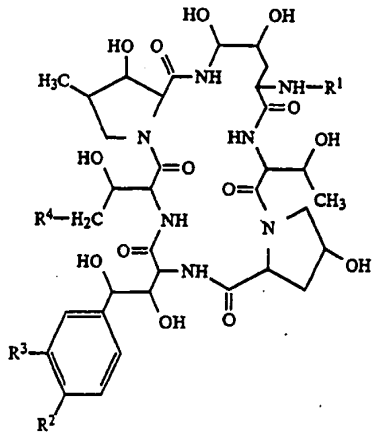
Accordingly, one object of the present invention is to provide the polypeptide compound and a pharmaceutically acceptable salt thereof, which are highly active against a number of pathogenic microorganisms in human being and animals.

Another object of the present invention is to provide a process for the preparation of the polypeptide compound and a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said polypeptide compound or a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a method for treating or preventing infectious diseases caused by pathogenic microorganisms, which comprises administering said polypeptide compound to human being or animals.

The object polypeptide compound of the present invention is novel and can be represented by the following general formula [I] (SEQ ID NO: 1):



[I]

wherein

R^1 is hydrogen or acyl group,

R^2 is hydroxy or acyloxy,

R^3 is hydrogen or hydroxysulfonyloxy, and

R^4 is hydrogen or carbamoyl,

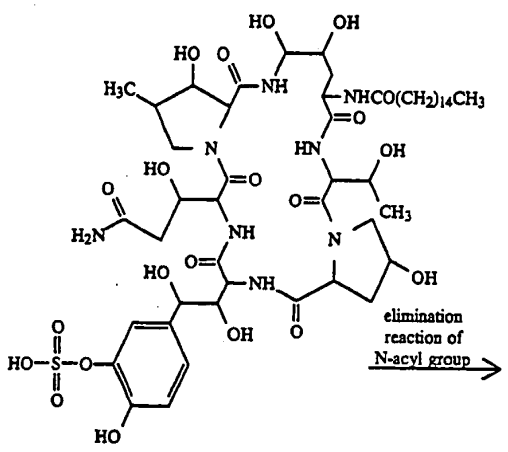
with proviso that

(i) R^2 is acyloxy, when R^3 is hydrogen, and

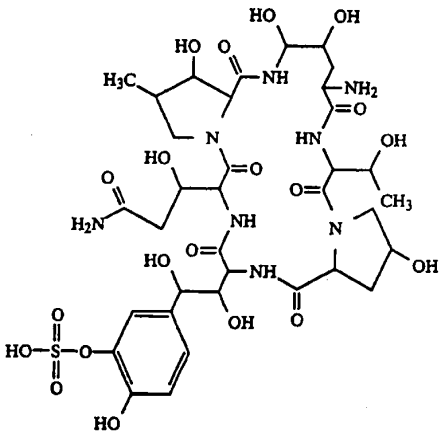
(ii) R^1 is not palmitoyl, when R^2 is hydroxy, R^3 is hydroxysulfonyloxy and R^4 is carbamoyl.

The polypeptide compound [I] (SEQ ID NO: 1) of the present invention can be prepared by the processes as illustrated in the following schemes.

Process 1

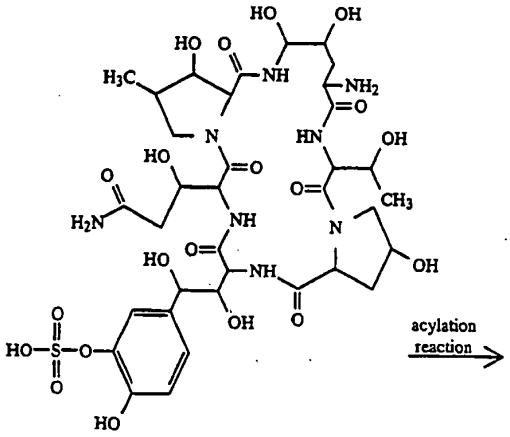


[II] (SEQ ID NO: 1) or a salt thereof



[Ia] (SEQ ID NO: 1) or a salt thereof

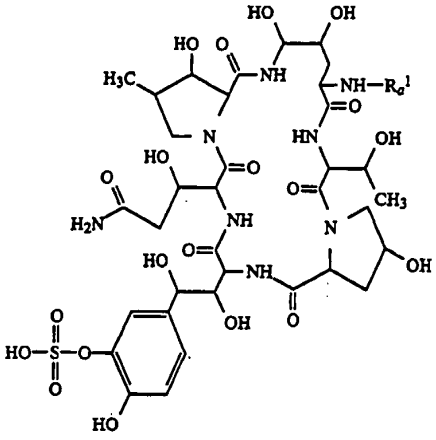
Process 2



[Ia] (SEQ ID NO: 1) or a salt thereof

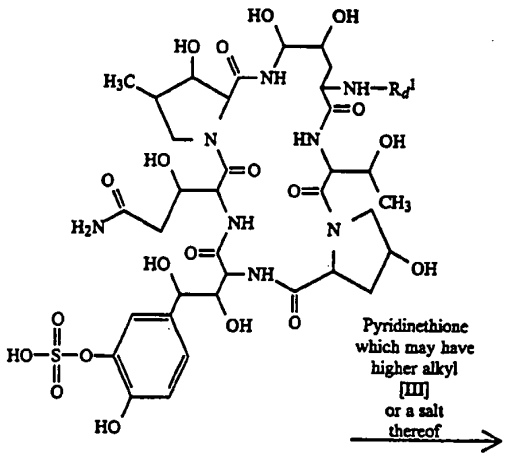
-continued

Process 2



[Ib] (SEQ ID NO: 1)
or a salt thereof

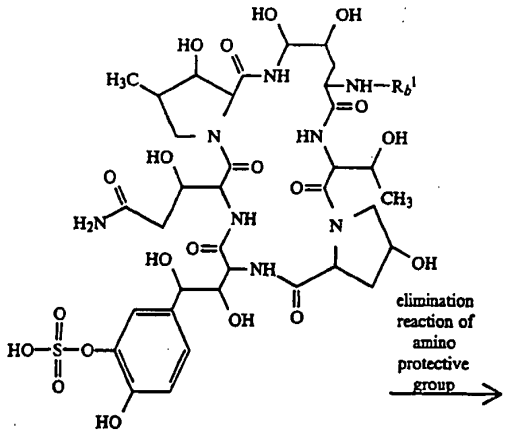
Process 4



Pyridinethione which may have higher alkyl [III] or a salt thereof

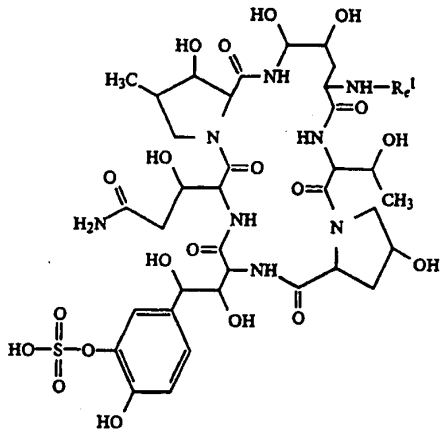
[Ie] (SEQ ID NO: 1)
or a salt thereof

Process 3



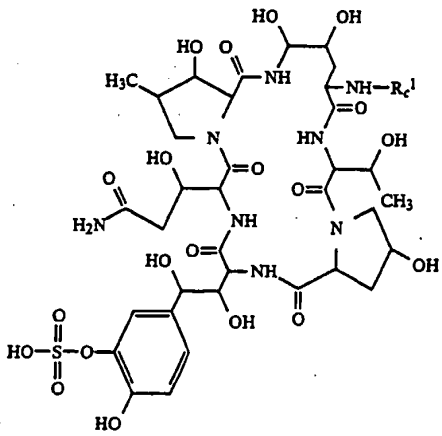
elimination reaction of amino protective group

[Ic] (SEQ ID NO: 1)
or a salt thereof

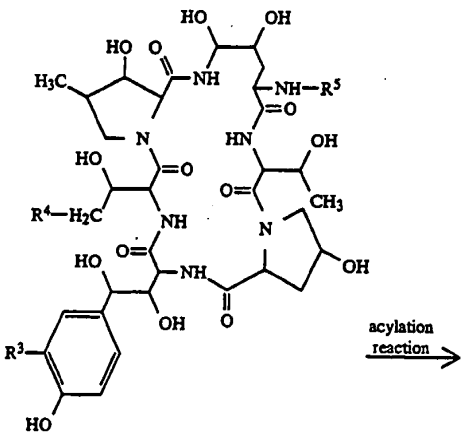


[If] (SEQ ID NO: 1)
or a salt thereof

Process 5



[Id] (SEQ ID NO: 1)
or a salt thereof

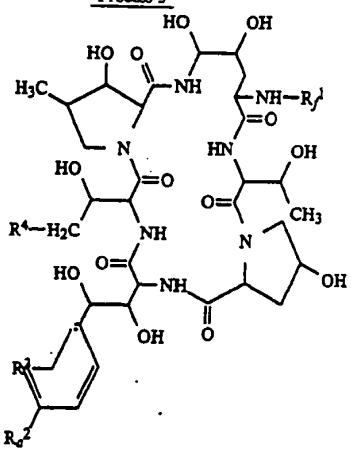


acylation reaction

[IV] (SEQ ID NO: 1)
or a salt thereof

-continued

Process 5



[Ig] (SEQ ID NO: 1)
or a salt thereof

wherein

R^3 and R^4 are each as defined above,

R_a^1 is acyl group exclusive of palmitoyl,

R_b^1 is ar(lower)alkanoyl which has higher alkoxy and protected amino,

R_c^1 is ar(lower)alkanoyl which has higher alkoxy and amino,

R_d^1 is halo(lower)alkanoyl,

R_e^1 is pyridylthio(lower)alkanoyl which may have higher alkyl,

R_f^1 is acyl,

R_a^2 is acyloxy, and

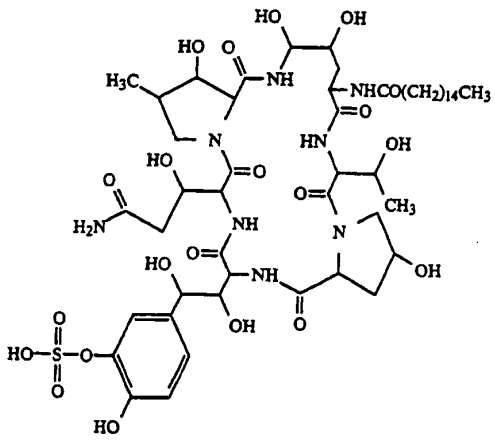
R^5 is acyl group.

The starting compound [II] (SEQ ID NO: 1) or a salt thereof is novel and can be prepared by the following fermentation process.

Process A

A strain belonging to the Coleophoma which is capable of producing the compound [II] or a salt thereof

fermentation →



[II] (SEQ ID NO: 1)
or a salt thereof

Some of the starting compound [IV] are novel and can be prepared according to the aforesaid Process 1 to 4.

Suitable pharmaceutically acceptable salt of the object compound [I] (SEQ ID NO: 1) is conventional non-toxic mono or di salts and include a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, etc.] an organic acid addition salt [e.g. formate, acetate, trifluroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid addition salt e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc.], a salt with an amino acid [e.g. arginine salt, aspartic acid salt, glutamic acid salt, etc.], and the like.

In the above and subsequent description of this specification, suitable examples of the various definitions are explained in detail as follows:

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

The term "higher" is intended to mean 7 to 20 carbon atoms, unless otherwise indicated.

Suitable "acyl group" may be aliphatic acyl, aromatic acyl, heterocyclic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid, sulfonic acid, and the like.

Suitable example of the "acyl group" thus explained may be:

lower alkanoyl [e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, hexanoyl, pivaloyl, etc.] which may have one or more (preferably 1 to 3) suitable substituent(s) such as halogen (e.g. fluoro, chloro, bromo, iodo); aryl (e.g. phenyl, naphthyl, anthryl, etc.) which may have one or more (preferably 1 to 3) suitable substituent(s) like hydroxy, higher alkoxy as explained below, aforesaid aryl, or the like; lower alkoxy as explained below; amino; protected amino, preferably, acylamino such as lower alkoxycarbonylamino (e.g. methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, t-butoxycarbonylamino, pentyloxycarbonylamino, hexyloxycarbonylamino, etc.); or the like; di(lower)alkylamino (e.g. dimethylamino, N-methylethylamino, diethylamino, N-propylbutylamino, dipentylamino, dihexylamino, etc.); lower alkoxyimino (e.g. methoxyimino, ethoxyimino, propoxyimino, butoxyimino, t-butoxyimino, pentyloxyimino, hexyloxyimino, etc.); ar(lower)alkoxyimino such as phenyl(lower)alkoxyimino (e.g. benzyloxyimino, phenethyloxyimino, benzhydryloxyimino, etc.) which may have one or more (preferably 1 to 3) suitable substituent(s) like higher alkoxy as explained below, or the like; heterocyclicthio, preferably, pyridylthio, which may have one or more (preferably 1 to 3) suitable substituent(s) like higher alkyl (e.g. heptyl, octyl, 2-ethylhexyl, nonyl, decyl, 3,7-dimethyloctyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, 3-methyl-10-ethyldodecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, etc.), or the like; heterocyclic group (e.g. thienyl, imidazolyl, pyrazolyl, furyl, tetrazolyl, thiazolyl, thiadiazolyl, etc.) which may have one or more (preferably 1 to 3) suitable substituent(s) like amino, aforesaid protected amino, aforesaid higher alkyl, or the like; or the like;

higher alkanoyl [e.g. heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, lauroyl, tridecanoyl, myristoyl,

pentadecanoyl, palmitoyl, 10,12-dimethyltetradecanoyl, heptadecanoyl, stearoyl, nonadecanoyl, icosanoyl, etc.];

lower alkenoyl [e.g. acryloyl, methacryloyl, crotonoyl, 3-pentenoyl, 5-hexenoyl, etc.] which may have one or more (preferably 1 to 3) suitable substituent(s) such as aforesaid aryl which may have one or more (preferably 1 to 3) suitable substituent(s) like higher alkoxy as explained below, or the like, or the like;

higher alkenoyl [e.g. 4-heptenoyl, 3-octenoyl, 3,6-decadienoyl, 3,7,11-trimethyl-2,6,10-dodecatrienoyl, 4,10-heptadecadienoyl, etc.];

lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.];

higher alkoxycarbonyl [e.g. heptyloxycarbonyl, octyloxycarbonyl, 2-ethylhexyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, 3,7-dimethyloctyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, tridecyloxycarbonyl, tetradecyloxycarbonyl, pentadecyloxycarbonyl, 3-methyl-10-ethyldodecyloxycarbonyl, hexadecyloxycarbonyl, heptadecyloxycarbonyl, octadecyloxycarbonyl, nonadecyloxycarbonyl, icosyloxycarbonyl, etc.];

aryloxycarbonyl [e.g. phenoxycarbonyl, naphthyloxycarbonyl, etc.];

arylglyoxyloyl [e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc.];

ar(lower)alkoxycarbonyl which may have one or more suitable substituent(s) such as phenyl(lower)alkoxycarbonyl which may have nitro or lower alkoxy [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, etc.];

lower alkylsulfonyl [e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, pentylsulfonyl, butylsulfonyl, etc.];

arylsulfonyl [e.g. phenylsulfonyl, naphthylsulfonyl, etc.] which may have one or more (preferably 1 to 3) suitable substituent(s) such as lower alkyl as explained below, higher alkoxy as explained below, or the like;

ar(lower)alkylsulfonyl such as phenyl(lower)alkylsulfonyl [e.g. benzylsulfonyl, phenethylsulfonyl, benzhydrylsulfonyl, etc.], or the like;

aroyl [e.g. benzoyl, naphthoyl, anthrylcarbonyl, etc.] which may have one or more (preferably 1 to 5) suitable substituent(s) such as aforesaid halogen; lower alkyl (e.g. methyl, ethyl, propyl, butyl, t-butyl, pentyl, hexyl, etc.); aforesaid higher alkyl; lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, t-butoxy, pentyloxy, hexyloxy, etc.) which may have one or more (preferably 1 to 10) suitable substituent(s) like aforesaid lower alkoxy, aforesaid halogen, aforesaid aryl, or the like; higher alkoxy (e.g. heptyloxy, octyloxy, 2-ethylhexyloxy, nonyloxy, decyloxy, 3,7-dimethyloctyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, pentadecyloxy, 3-methyl-10-ethyldodecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, icosyloxy, etc.) which may have one or more (preferably 1 to 17) suitable substituent(s) like aforesaid halogen; higher alkenyloxy (e.g. 3-heptenyloxy, 7-octenyloxy, 2,6-octadienyloxy, 5-nonenyloxy, 1-decenyloxy, 3,7-dimethyl-6-octenyloxy, 3,7-dimethyl-2,6-octadienyloxy, 8-undecenyloxy, 3,6,8-dodecatrienyloxy, 5-tridecenyloxy, 7-tetradecenyloxy, 1,8-pentadecadienyloxy, 15-hexadecenyloxy, 11-heptadecenyloxy, 7-octadecenyloxy, 10-nonadecenyloxy, 18-icosenyloxy, etc.); carboxy; aforesaid aryl which may have one or more (preferably 1 to 3) suitable substituent(s) like aforesaid higher alkoxy; aryloxy (e.g. phenoxy, naphthyloxy, anthryloxy, etc.) which may have one or more (preferably 1 to 3) suitable substituent(s) like aforesaid lower alkoxy, or aforesaid higher alkoxy; or the like; or the like.

In said "acyl group", the preferred one may be lower alkanoyl; halo(lower)alkanoyl;

ar(lower)alkanoyl which may have one or more (preferably 1 to 3) hydroxy, lower alkoxy, higher alkoxy, aryl, amino, protected amino, di(lower)alkylamino, lower alkoxyimino or ar(lower)alkoxyimino which may have one or more (preferably 1 to 3) higher alkoxy;

heterocyclicthio(lower)alkanoyl which may have one or more (preferably 1 to 3) higher alkyl;

heterocyclic(lower)alkanoyl which may have one or more (preferably 1 to 3) lower alkoxyimino, higher alkyl, amino or protected amino;

ar(lower)alkoxyimino(lower)alkanoyl which may have one or more (preferably 1 to 3) higher alkoxy;

higher alkanoyl;

ar(lower)alkenoyl which may have one or more (preferably 1 to 3) higher alkoxy;

higher alkenoyl; lower alkoxycarbonyl; higher alkoxycarbonyl; aryloxycarbonyl;

arylsulfonyl which may have one or more (preferably 1 to 3) lower alkyl or higher alkoxy;

aroyl which may have one or more (preferably 1 to 5) halogen, lower alkyl, higher alkyl, carboxy, lower alkoxy which may have one or more (preferably 1 to 10) halogen, lower alkoxy(lower)alkoxy, ar(lower)alkoxy, higher alkoxy which may have one or mare (preferably 1 to 17) halogen, higher alkenyloxy, aryl which may have one or more (preferably 1 to 3) higher alkoxy or aryloxy which may have one or more (preferably 1 to 3) lower alkoxy or higher alkoxy;

in which the more preferred one may be lower alkanoyl; halo(lower)alkanoyl;

phenyl(lower)alkanoyl or naphthyl(lower)alkanoyl, each of which may have 1 to 3 hydroxy, lower alkoxy, higher alkoxy, phenyl, amino, lower alkoxycarbonylamino, di(lower)alkylamino, lower alkoxyimino, or phenyl(lower)alkoxyimino which may have 1 to 3 higher alkoxy;

pyridylthio(lower)alkanoyl which may have 1 to 3 higher alkyl;

imidazolyl(lower)alkanoyl or thiazolyl(lower)alkanoyl, each of which may have 1 to 3 lower alkoxyimino, higher alkyl, amino or lower alkoxycarbonylamino;

phenyl(lower)alkoxyimino(lower)alkanoyl which may have 1 to 3 higher alkoxy;

higher alkanoyl;

phenyl(lower) alkenoyl which may have 1 to 3 higher alkoxy;

higher alkenoyl; lower alkoxycarbonyl, higher alkoxycarbonyl; phenoxycarbonyl;

phenylsulfonyl or naphthylsulfonyl, each of which may have 1 to 3 lower alkyl or higher alkoxy;

benzoyl, naphthoyl or anthrylcarbonyl, each of which may have 1 to 5 halogen, lower alkyl, higher alkyl, carboxy, lower alkoxy which may have 6 to 10 halogen, lower alkoxy(lower)alkoxy, phenyl(lower)alkoxy, higher alkoxy which may have 12 to 17 halogen, higher alkenyloxy, phenyl which may have 1 to 3 higher alkoxy, phenoxy which may have 1 to 3 lower alkoxy or higher alkoxy;

the much more preferred one may be (C_1–C_4)alkanoyl; halo(C_1–C_4)alkanoyl;

phenyl(C_1-C_4)alkanoyl which may have 1 to 3 hydroxy, (C_1-C_4)alkoxy, (C_7-C_{16})alkoxy, phenyl, amino, (C_1-C_4)alkoxycarbonylamino, di(C_1-C_4)alkylamino, (C_1-C_4)alkoxyimino or phenyl(C_1-C_4)alkoxyimino which may have (C_7-C_{16})alkoxy;

naphthyl (C_1-C_4)alkanoyl which may have 1 to 3 (C_1-C_4)alkoxycarbonylamino;

1-(C_7-C_{16})alkylpyridiniothio (C_1-C_4)alkanoyl;

imidazolyl(C_1-C_4)alkanoyl which may have 1 to 3 (C_7-C_{16}) alkyl or (C_1-C_4)alkoxycarbonylamino;

thiazolyl(C1-C4)alkanoyl which may have 1 to 3 (C_1-C_4)alkoxyimino or amino;

phenyl(C_1-C_4)alkoxyimino(C1-C_4)alkanoyl which may have 1 to 3 (C_7-C_{16})alkoxy;

(C_7-C_{17})alkyl;

phenyl(C_1-C_4)alkenoyl which may have 1 to 3 (C_7-C_{16})alkoxy;

(C_7-C_{18})alkenoyl; (C_3-C_6)alkoxycarbonyl; (C_7-C_{16})alkoxycarbonyl; phenoxycarbonyl;

phenylsulfonyl which may have (C_1-C_4)alkyl or (C_7-C_{16})alkoxy;

naphthylsulfonyl which may have (C_7-C_{16})alkoxy;

benzoyl which may have 1 to 5 halogen, (C_3-C_6)alkyl, (C_7-C_{16})alkyl, carboxy, (C_1-C_6)alkoxy which may have 6 to 10 halogen, (C_1-C_4)alkoxy(C_1-C_4)alkoxy, phenyl (C_3-C_6)alkoxy, (C_7-C_{16})alkoxy which may have 12 to 17 halogen, phenyl which may have 1 to 3 (C_7-C_{16})alkoxy or phenoxy which may have 1 to 3 (C_3-C_6)alkoxy or (C7-C16)alkoxy;

naphthoyl which may have 1 to 3 (C_3-C_6)alkoxy, (C_7-C_{16})alkoxy or (C_7-C_{16})alkenyloxy;

anthrylcarbonyl;

and the most preferred one may be acetyl, 2-bromoacetyl, 2-(4-biphenylyl)acetyl, 2-(4-octyloxyphenyl)acetyl, 3-(4-octyloxyphenyl)propionyl, 2-amino-2-(4-octyloxyphenyl)acetyl, 2-(t-butoxycarbonylamino)-2-(4-octyloxyphenyl)acetyl, 2-amino-3-(4-octyloxyphenyl)propionyl, 2-(t-butoxycarbonylamino)-3-(4-octyloxyphenyl)propionyl, 2-dimethylamino-3-(4-octyloxyphenyl)propionyl, 2-(t-butoxycarbonylamino)-2-(2-naphthyl)acetyl, 2-methoxy-2-(4-octyloxyphenyl-)acetyl, 2-methoxyimino-2-(4-octyloxyphenyl)acetyl, 2-(4-octyloxybenzyloxyimino)-2-(4-hydroxyphenyl)acetyl, 2-(4-octyloxybenzyloxyimino)-2-phenylacetyl, 2-(4-octyloxybenzyloxyimino)acetyl, 2-(1-octyl-4-pyridinio)thioacetyl, 2-methoxyimino-2-(2-aminothiazol-4-yl)acetyl, 2-(t-butoxycarbonylamino)-3-(1-octyl-4-imidazolyl)propionyl, 3-(4-octyloxyphenyl)acryloyl, 3,7,11-trimethyl-2,6,10-dodecatrienoyl, t-butoxycarbonyl, octyloxycarbonyl, phenoxycarbonyl, p-tolylsulfonyl, 4-octyloxyphenylsulfonyl, 6-octyloxy-2-naphthylsulfonyl, 4-(t-butyl)benzoyl, 4-octylbenzoyl, 2,3,5,6-tetrafluoro-4-(2,2,3,3,4,4,5,5-octafluoropentyloxy)benzoyl, 4-(2-butoxyethoxy)benzoyl, 4-(4-phenylbutoxy)benzoyl, 4-octyloxybenzoyl, 2-carboxy-4-octyloxybenzoyl, 3-methoxy-4-octyloxybenzoyl, 4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyloxy)-2,3,5,6-tetrafluorobenzoyl, 4-(4-octyloxyphenyl)benzoyl, 4-(4-octyloxyphenoxy)benzoyl, 6-butoxy-2-naphthoyl, 6-hexyloxy-2-naphthoyl, 6-octyloxy-2-naphthoyl, 6-(2-ethylhexyloxy)-2-naphthoyl, 6-decyloxy-2-naphthoyl, 6-(3,7-dimethyloctyloxy)-2-naphthoyl, 6-dodecyloxy-2-naphthoyl, 6-(3,7-dimethyl-6-octenyloxy)-2-naphthoyl, 6-(3,7-dimethyl-2,6-octadienyloxy)-2-naphthoyl, 2-anthrylcarbonyl), 4-(4-heptyloxyphenyl)-benzoyl and 4-(4-hexyloxyphenoxy)benzoyl.

Suitable "acyl group exclusive of palmitoyl" can be referred to the ones as exemplified before for "acyl group" except palmitoyl.

Suitable "ar(lower)alkanoyl" moiety in "ar(lower)alkanoyl which has higher alkoxy and protected amino" and "ar(lower)alkanoyl which has higher alkoxy and amino" can be referred to the ones as exemplified before for "acyl group" and suitable examples of the substituent(s) "higher alkoxy" and "protected amino" can be referred to the ones as exemplified before for "acyl group".

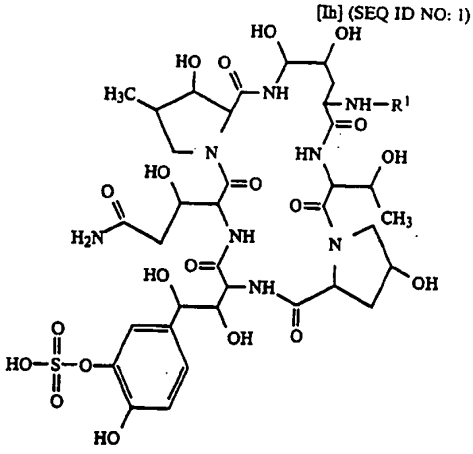
Suitable "halo(lower)alkanoyl" can be referred to the ones as exemplified before for "acyl group".

Suitable "pyridylthio(lower)alkanoyl" in "pyridylthio(lower)alkanoyl which may have higher alkyl" can be referred to the ones as exemplified before for "acyl group", and suitable examples of the substituent "higher alkyl" can be exemplified before for "acyl group".

Suitable "acyloxy" may include hydroxysulfonyloxy, phosphonooxy, and the like.

In the object compound [I] (SEQ ID NO: 1) thus defined, the following compound [I] is especially preferable.

[Ih] (SEQ ID NO: 1)



[II] (SEQ ID NO: 1)
or a salt thereof

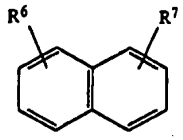
wherein R^1 is hydrogen or acyl group, with proviso that R^1 is not palmitoyl.

Suitable "acylating agent" for the acylation reaction is Process 2 may be an acid compound corresponding to the acyl group to be introduced or its reactive derivative at the carboxy group or a salt thereof and suitable example of said acylating agent is represented by the formula:

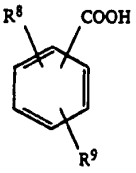
$$R_a^1\text{—OH} \qquad [V]$$

wherein R_a^1 is as defined above or its reactive derivative at the carboxy group or a salt thereof.

In the compound [V], the following compounds are novel.



[V-1]
or its reactive derivative
at the carboxy group
or a salt thereof



[V-2]
or its reactive derivative
at the carboxy group
or a salt thereof

wherein R^6 is lower alkoxy, higher alkoxy or higher alkenyloxy,

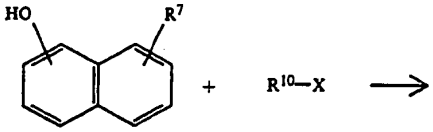
$R^7$is —COOH or —SO_3H,

R^8 is 1 to 4 halogen,

R^9 is lower alkoxy which has one or more halogen, higher alkoxy which has one or more halogen.

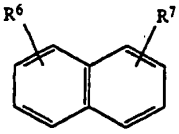
The compounds [V-1] and [V-2] can be prepared by the following processes.

Process B



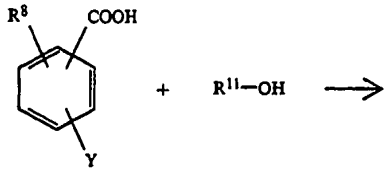
[VI]
or a salt thereof

[VII]
or a salt thereof



[V-1]
or a salt thereof

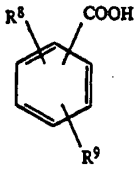
Process C



[VIII]
or a salt thereof

[IX]
or a salt thereof

-continued



[V-2]
or a salt thereof

wherein R^6, R^7, R^8 and R^9 are each as defined above

R^{10} is lower alkyl, higher alkyl or higher alkenyl,

R^{11} is lower alkyl which has one or more halogen or higher alkyl which has one or more halogen, and

X and Y are each a leaving group.

In the above definitions, suitable "lower alkoxy", "higher alkoxy", "higher alkenyloxy", "halogen", "lower alkyl" and "higher alkyl" can be referred to the ones as exemplified before.

Suitable "higher alkenyl" may include 3-heptenyl, 7-octenyl, 2,6-octadienyl, 5-nonenyl, 1-decenyl, 3,7-dimethyl-6-octenyl, 3,7-dimethyl-2,6-octadienyl, 8-undecenyl, 3,6,8-dodecatrienyl, 5-tridecenyl, 7-tetradecenyl, 1,8-pentadecadienyl, 15-hexadecenyl, 11-heptadecenyl, 7-octadecenyl, 10-nonadecenyl, 18-icosenyl and the like, in which the preferred one may be (C_7-C_{16})alkenyl.

As for R^9, "lower alkoxy" has one or more (preferably 1 to 10, more preferably 6 to 10) halogen, and "higher alkoxy" has one or more (preferably 1 to 17, more preferably 12 to 17) halogen.

As for R^{11}, "lower alkyl" has one or more (preferably 1 to 10, more preferably 6 to 10) halogen, and "higher alkyl" has one or more (preferably 1 to 17, more preferably 12 to 17)halogen.

As for R^6, preferred "lower alkoxy" may be (C_4-C_6-)alkoxy.

Suitable "a leaving group" may include aforesaid halogen, lower alkanoyloxy (e.g. acetoxy, etc.), sulfonyloxy (e.g. mesyloxy, tosyloxy, etc.), and the like.

Regarding suitable salts and the reactive derivatives at the carboxy group of the compounds [V-1] and [V-2], they can be referred to the ones as exemplified below for the compound [V].

The reactions in Processes B and C can be carried out according to the methods disclosed later in Preparations of the present specification or the similar manners thereto.

In the compound [V], there are other novel compounds than compounds [V-1] and [V-2], and they can be prepared, for example, by the methods disclosed later in Preparations.

Suitable "pyridinethione" in Process 4 may include 1,2-dihydropyridine-2-thione, 1,4-dihydropyridine-4-thione, and the like, and said "pyridinethione" may have aforesaid "higher alkyl".

The processes for preparing the object compound [I] or a salt thereof of the present invention are explained in detail in the following.

PROCESS 1

The object compound [Ia] (SEQ ID NO: 1) or a salt thereof can be prepared by subjecting a compound [II] (SEQ ID NO: 1) or a salt thereof to elimination reaction of N-acyl group.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction, reaction with an enzyme or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used-in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

The reaction with an enzyme can be carried out by reacting the compound [II] (SEQ ID NO: 1) or a salt thereof with an enzyme suitable for the elimination reaction of N-acyl group.

Suitable example of said enzyme may include the one produced by certain microorganisms of the Actinoplanaceae, for example, Actinoplanes utahensis IFO-13244, Actinoplanes utahensis ATCC 12301, Actinoplanes missourienses NRRL 12053, or the like; and the like.

This elimination reaction is usually carried out in a solvent such as phosphate buffer, Tris-HCl buffer or any other solvent which does not adversely influence the reaction

The reaction temperature is not critical and the reaction can be carried out at room temperature or under warming.

PROCESS 2

The object compound [Ib] (SEQ ID NO: 1) or a salt thereof can be prepared by subjecting the compound [Ia] (SEQ ID NO: 1) or a salt thereof to acylation reaction.

The acylation reaction of this process can be carried out by reacting the compound [Ia] (SEQ ID NO: 1) or a salt thereof with aforesaid "acylating agent", for example, the compound [V] (SEQ ID NO: 1) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound [V] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivaric acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.]; or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+{=}CH{-}$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound [V] (SEQ ID NO: 1) to be used.

Suitable salts of the compound [V] (SEQ ID NO: 1) and its reactive derivative can be referred to the ones as exemplified for the compound [I] (SEQ ID NO: 1).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the

reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [V] (SEQ ID NO: 1) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, methanesulfonyl chloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, di(lower)alkylaminopyridine (e.g. 4-dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

PROCESS 3

The object compound [id] (SEQ ID NO: 1) or a salt thereof can be prepared by subjecting a compound [Ic] (SEQ ID NO: 1) or a salt thereof to elimination reaction of amino protective group.

Suitable salts of the compounds [Ic] (SEQ ID NO: 1) and [Id] (SEQ ID NO: 1) can be referred to the ones as exemplified for the compound [I] (SEQ ID NO: 1).

This elimination reaction can be carried out in accordance with a conventional method as explained above for Process 1.

PROCESS 4

The object compound [If] (SEQ ID NO: 1) or a salt thereof can be prepared by reacting a compound [Ie] (SEQ ID NO: 1) or a salt thereof with a compound [III] (SEQ ID NO: 1) or a salt thereof.

Suitable salt of the compound [If] (SEQ ID NO: 1) can be referred to the ones as exemplified for the compound [I] (SEQ ID NO: 1).

Suitable salt of the compound [III] (SEQ ID NO: 1) can be referred to acid addition salts as exemplified for the compound [I] (SEQ ID NO: 1).

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, methanol, ethanol, diethyl ether, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound [III] (SEQ ID NO: 1) is in liquid, it can also be used as a solvent.

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, organic base such as trialkylamine, and the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at room temperature, under warming or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium iodide, potassium iodide, etc.], alkali metal thiocyanate [e.g. sodium thiocyanate, potassium thiocyanate, etc.] or the like.

PROCESS 5

The object compound [Ig] (SEQ ID NO: 1) or a salt thereof can be prepared by subjecting a compound [IV] (SEQ ID NO: 1) or a salt thereof to acylation reaction.

Suitable salts of the compounds [Ig] (SEQ ID NO: 1) and [IV] (SEQ ID NO: 1) can be referred to the ones as exemplified for the compound [I] (SEQ ID NO: 1).

Suitable "acylating agent" in this Process 5 may be an acid compound corresponding to the acyl group to be introduced, for example, phosphoric acid and its derivative (e.g. phosphoryl chloride, diphenylphosphorochloridate, etc.), sulfuric acid and its derivative [e.g. sulfur trioxide-pyridine, sulfur trioxidetri(lower)alkylamine (e.g. trimethylamine, triethylamine, etc.), chlorosulfonic acid, etc.], or the like.

This reaction can be carried out in a conventional manner.

The process for preparing the starting compound [II] (SEQ ID NO: 1) or a salt thereof of the present invention is explained in detail in the following.

PROCESS A

The compound [II] (SEQ ID NO: 1) or a salt thereof can be prepared by the fermentation process.

The fermentation process is explained in detail in the following.

The compound [II] (SEQ ID NO: 1) or a salt thereof of this invention can be produced by fermentation of the compound [II] (SEQ ID NO: 1) or a salt thereof-producing strain belonging to the genus Coleophoma such as Coleophoma sp. F-11899 in a nutrient medium.

(i) Microorganism:

Particulars of the microorganism used for producing the compound [II] (SEQ ID NO: 1) or a salt thereof is explained in the following.

The strain F-11899 was originally isolated from a soil sample collected at Iwaki-shi, Fukushima-ken, Japan. This organism grew rather restrictedly on various culture media, and formed dark grey to brownish grey colonies. Anamorph (conidiomata) produced on a steam-sterilized leaf segment affixed on a Miura's LCA plate[1)] or a corn meal agar plate by inoculating the isolate, while neither teleomorph nor anamorph formed on the agar media. Its morphological, cultural and physiological characteristics are as follows.

1) Miura, K. and M. Y. Kudo: An agar-medium for aquatic Hyphomycetes., Trans. Ycolo. Soc. Japan, 11:116-118, 1970.

Cultural characteristics on various agar media are summarized in Table 1. Cultures on potato dextrose agar grew rather rapidly, attaining 3.5–4.0 cm in diameter after two weeks at 25° C. This colony surface was plane, felty, somewhat wrinkly and brownish grey. The

colony center was pale grey to brownish grey, and covered with aerial hyphae. The reverse color was dark grey. Colonies on malt extract agar grew more restrictedly, attaining 2.5–3.0 cm in diameter under the same conditions. The surface was plane, thin to felty and olive brown. The colony center was yellowish grey, and covered with aerial hyphae. The reverse was brownish grey.

The morphological characteristics were determined on basis of the cultures on a sterilized leaf affixed to a Miura's LCA plate. Conidiomata formed on the leaf segment alone. They were pycnidial, superficial, separate, discoid to ampulliform, flattened at the base, unilocular, thin-walled, black, 90–160(−200) μm in diameter and 40–70 μm high. Ostiole was often single, circular, central, papillate, 10–30 μm in diameter and 10–20 μm high. Conidiophores formed from the lower layer of inner pycnidial walls. They were hyaline, simple or sparingly branched, septate and smooth. Conidiogenous cells were enteroblastic, phialidic, determinate, ampulliform to obpyriform, hyaline, smooth, 5–8×4–6 μm, with a collarette. The collarettes were campanulate to cylindrical, and 14–18×3–5 μm. Conidia were hyaline, cylindrical, thin-walled, aseptate, smooth and 14–16(−18)×3–3 μm.

The vegetative hyphae were septate, brown, smooth and branched. The hyphal cells were cylindrical and 2–7 μm thick. The chlamydospores were absent.

The strain F-11899 had a temperature range for growth of 0° to 31° C. and an optimum temperature of 23° to 27° C. on potato dextrose agar.

The above characteristics indicate that the strain F-11899 belongs to the order Coelomycetes[2), 3), 4)]. Thus, we named the strain "Coelomycetes strain F-11899".

2) Arx, J. A. von: The Genera of Fungi—Sporulating in Pure Culture (3rd ed.), 315 p., J. Cramer, Vaduz, 1974.
3) Sutton, B. C.: The Coelomycetes—Fungi Imperfecti with Pycnidia, Acervuli and Stromata., 696 p., Commonwealth Mycological Institute, Kew, 1980.
4) Hawksworth, D. L., B. C. Sutton and G. C. Ainsworth: Dictionary of the Fungi (7th ed.), 445 p., Commonwealth Mycological Institute, Kew., 1983.

TABLE 1

Medium	Cultural characteristics of the strain F-11899
Malt extract agar (Blakeslee 1915)	G: Rather restrictedly, 2.5–3.0 cm S: Circular, plane, thin to felty, olive brown (4F5), arising aerial hyphae at the center (yellowish grey (4B2)) R: Brownish grey (4F2)
Potato dextrose agar (Difco 0013)	G: Rather rapidly, 3.5–4.0 cm S: Circular, plane, felty, somewhat wrinkly, brownish grey (4F2), arising aerial hyphae at the center (pale grey (4B1) to brownish grey (4F2)) R: Dark grey (4F1)
Czapeck's solution agar (Raper and Thom 1949)	G: Very restrictedly, 1.0–1.5 cm S: Irregular, thin, scanty, immersed, subhyaline to white. R: Subhyaline to white
Sabouraud dextrose agar (Difco 0109)	G: Restrictedly, 2.0–2.5 S: Circular, plane, thin, white, sectoring, light brown (6D5) at the colony center R: Pale yellow (4A3)
Oatmeal agar (Difco 0552)	G: Fairly rapidly, 4.0–4.5 cm S: Circular, plane, felty to cottony, dark grey (4F1) to brownish grey (4F2) R: Brownish grey (4D2)
Emerson Yp Ss agar (Difco 0739)	G: Restrictedly, 2.0–2.5 cm S: Circular to irregular, plane,

TABLE 1-continued

Medium	Cultural characteristics of the strain F-11899
	felty, dark grey (4F1) to brownish grey (4F2) R: Medium grey (4E1) to dark grey (4F1)
Corn meal agar (Difco 0386)	G: Rather restrictedly, 2.5–3.0 cm S: Circular, plane, thin to felty, dark grey (2F1) to olive (2F3) R: Dark grey (2P1) to olive (2F3)
MY20 agar	G: Restrictedly, 1.5–2.0 cm S: Circular to irregular, thin, sectoring, yellowish white (4A2) R: Pale yellow (4A3) to orange white (5A2)

Abbreviations:
G: growth, measuring colony size in diameter
S: colony surface
R: reverse

These characteristics were observed after 14 days of incubation at 25° C. The color descriptions were based on the Methuen Handbook of Colour[5)].

5) Kornerup, A. and Wanscher, J. H.: Methuen Handbook of Colour (3rd ed.), 252 p., Methuen, London, 1983.

A culture of Coelomycetes strain F-11899 thus named has been deposited with the Fermentation Research Institute Agency of Industrial Science and Technology (1-3, Higashi 1 chome, Tsukuba-shi, IBARARKI 305 JAPAN) on Oct. 26, 1989 under the number of FERM BP-2635.

After that, however, we have further studied the classification of the strain F-11899, and have found that the strain F-11899 resembled *Coleophoma empetri* (Rostrup) Petrak 1929 2), 3), 4) belonging to the order Coelomycetes, but differed in some pycnidial characteristics: globose or flattened at the base, immersed, and not papillate.

Considering these characteristics, we classified this strain in more detail and renamed it as "Coleophoma sp. F-11899".

In this connection, we have already taken step to amend the name, "Coelomycetes strain F-11899" to Coleophoma sp. F-11899 with the Fermentation Research Institute Agency of Industrial Science and Technology on Sep. 21, 1990.

(ii) Production of the compound [II] (SEQ ID NO: 1) or a salt thereof

The compound [II] (SEQ ID NO: 1) or a salt thereof of this invention is produced when the compound [II] (SEQ ID NO: 1) or a salt thereof-producing strain belonging to the genus Coleophoma is grown in a nutrient medium containing sources of assimilable carbon and nitrogen under aerobic conditions (e.g. shaking culture, submerged culture, etc.).

The preferred sources of carbon in the nutrient medium are carbohydrates such as glucose, sucrose, starch, fructose or glycerin, or the like.

The preferred sources of nitrogen are yeast extract, peptone, gluten meal, cotton seed flour, soybean meal, corn steep liquor, dried yeast, wheat germ, etc., as well as inorganic and organic nitrogen compounds such as ammonium salts (e.g. ammonium nitrate, ammonium sulfate, ammonium phosphate, etc.), urea or amino acid, or the like.

The carbon and nitrogen sources, though advantageously employed in combination need not to he used in their pure form because less pure materials, which contain traces of growth factors and considerable quantities of mineral nutrients, are also suitable for use.

When desired, there may be added to the medium mineral salts such as sodium or calcium carbonate, sodium or potassium phosphate, sodium or potassium chloride, sodium or potassium iodide, magnesium salts, copper salts, zinc salt, or cobalt salts, or the like.

If necessary, especially when the culture medium foams seriously a defoaming agent, such as liquid paraffin, fatty oil, plant oil, mineral oil or silicone, or the like may be added.

As in the case of the preferred methods used for the production of other biologically active substances in massive amounts, submerged aerobic cultural conditions are preferred for the production of the compound [II] (SEQ ID NO: 1) or a salt thereof in massive amounts.

For the production in small amounts, a shaking or surface culture in a flask or bottle is employed.

Further, when the growth is carried out in large tanks, it is preferable to use the vegetative form of the organism for inoculation in the production tanks in order to avoid growth lag in the process of production of the compound [II] (SEQ ID NO: 1) or a salt thereof. Accordingly, it is desirable first to produce a vegetative inoculum of the organism by inoculating a relatively small quantity of culture medium with spores or mycelia of the organism and culturing said inoculated medium, and then to transfer the cultured vegetative inoculum to large tanks. The medium, in which the vegetative inoculum is produced, is substantially the same as or different from the medium utilized for the production of the compound [II] (SEQ ID NO: 1) or a salt thereof.

Agitation and aeration of the culture mixture may be accomplished in a variety of ways. Agitation may be provided by a propeller or similar mechanical agitation equipment, by revolving or shaking the fermentor, by various pumping equipment or by the passage of sterile air through the medium. Aeration may be effected by passing sterile air through the fermentation mixture.

The fermentation is usually conducted at a temperature between about 10° C. and 40° C., preferably 20° C. to 30° C., for a period of about 50 hours to 150 hours, which may be varied according to fermentation conditions and scales.

When the fermentation is completed, the culture broth is then subjected for recovery of the compound [II] (SEQ ID NO: 1) or a salt thereof to various procedures conventionally used for recovery and purification of biological active substances, for instance, solvent extraction with an appropriate solvent or a mixture of some solvents, chromatography or recrystallization from an appropriate solvent or a mixture of some solvents, or the like.

According to this invention, in general, the compound [II] (SEQ ID NO: 1) or a salt thereof is found both in the cultured mycelia and cultured broth. Accordingly, then the compound [II](SEQ ID NO: 1) or a salt thereof is removed from the whole broth by means of extraction using an appropriate organic solvent such as acetone or ethyl acetate, or a mixture of these solvents, or the like.

The extract is treated by a conventional manner to provide the compound [II](SEQ ID NO: 1) or a salt thereof, for example, the extract is concentrated by evaporation or distillation to a smaller amount and the resulting residue containing active material, i.e. the compound [II] (SEQ ID NO: 1) or a salt thereof is purified by conventional purification procedures, for example, chromatography or recrystallization from an appropriate solvent or a mixture of some solvents.

When the object compound is isolated as a salt of the compound [II](SEQ ID NO: 1), it can be converted to the free compound [II] (SEQ ID NO: 1) or another salt of the compound [II] (SEQ ID NO: 1) according to a conventional manner.

BIOLOGICAL PROPERTIES OF THE POLYPEPTIDE COMPOUND [I] (SEQ ID NO: 1) OF THE PRESENT INVENTION

In order to show the usefulness of the polypeptide compound [I] (SEQ ID NO: 1) of the present invention, some biological data of the representative compounds are explained in the following.

Test 1 Antimicrobial Activity (1):

Antimicrobial activity of the compound of Example 2 disclosed later (hereinafter referred to as FR131535 substance) was measured by micro-broth dilution method in 96 well multi-trays employing yeast nitrogen base dextrose medium. To a 50 μl sample solution with serial 2-fold dilution was added a 50 μl of microorganism suspension in saline to yield a final concentration of 1×10^5 colony forming units/ml. The Candida cultures were incubated at 37° C. for 22 hours. After incubation, the growth of microorganism in each well was determined by measuring the turbidity. The results were shown as IC_{50} value in which concentration the turbidity was half of that in the well without sample. The results are shown in Table 2.

TABLE 2

organism	IC_{50}
Candida albicans FP578	0.31
Candida tropicalis YC118	0.47

Test 2 Acute Toxicity of FR131535 Substance:

The acute toxicity of the FR131535 substance was determined to ICR mice (female, 4 weeks old) by a single intravenous injection. No toxic symptom was observed at the dose of 500 mg/kg.

Test 3 Antimicrobial Activity (2):

In vitro antimicrobial activity of the compound of Example 12 disclosed later (hereinafter referred to as FR139687 substance) was determined by the two-fold agar-plate dilution method as described below.

One loopful of an overnight culture of each test microorganism in Sabouraud broth containing 2% Glucose (10^5 viable cells per ml) was streaked on yeast nitrogen base dextrose agar (YNBDA) containing graded concentrations of the FR139687 substance, and the minimal inhibitory concentration (MIC) was expressed in terms of μg/ml after incubation at 30° C. for 24 hours.

organism	MIC (μg/ml)
Candida ablicans YU-1200	0.05

From the test results, it is realized that the polypeptide compound [I] (SEQ ID NO: 1) of the present invention has an anti-microbial activity (especially, antifungal activity).

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the polypeptide compound [I] (SEQ ID NO: 1) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. And, if necessary, in addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The polypeptide compound [I] (SEQ ID NO: 1) or a pharmaceutical acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired antimicrobial effect upon the process or condition of diseases.

For applying the composition to human, it is preferable to apply it by intravenous, intramuscular, pulmonary, or oral administration, or insufflation. While the dosage of therapeutically effective amount of the polypeptide compound [I] (SEQ ID NO: 1) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01–20 mg of the polypeptide compound [I] (SEQ ID NO: 1) per kg weight of human being, in the case of intramuscular administration, a daily dose of 0.1–20 mg of the polypeptide compound [I] (SEQ ID NO: 1) per kg weight of human being, in case of oral administration, a daily dose of 0.5–50 mg of the polypeptide compound [I] (SEQ ID NO: 1) per kg weight of human being is generally given for treating or preventing infectious diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To methanol (50 ml) was added thionyl chloride (8.73 ml) at −5° C. and the mixture was stirred for 10 minutes and then D-2-(p-hydroxyphenyl)glycine (5 g) was added thereto under ice-cooling. The mixture was stirred for 12 hours at room temperature. The reaction mixture was evaporated under reduced pressure to give D-2-(p-hydroxyphenyl)glycine methyl ester hydrochloride (6.3 g).

IR (Nujol): 3380, 1720, 1580, 1250 cm^{-1}

NMR (DMSO-d_6, δ): 3.70 (3H, s), 5.11 (1H, s), 6.83 (2H, d, J=8.6 Hz), 7.28 (2H, d, J=8.6 Hz), 8.91 (2H, s), 9.93 (1H, s)

Preparation 2

To a solution of D-2-(p-hydroxyphenyl)glycine methyl ester hydrochloride (6.3 g) and triethylamine (8.71 ml) in tetrahydrofuran (100 ml) was added di-t-butyl dicarbonate (6.82 g). The mixture was stirred for 2 hours at room temperature. The reaction mixture was added to diethyl ether (1 l) and an insoluble material was filtered off, and the filtrate was evaporated under reduced pressure to give N-(t-butoxycarbonyl)-D-2-(p-hydroxyphenyl)glycine methyl ester (6.83 g).

IR (Nujol): 3420, 3350, 1720, 1660 cm^{-1}

NMR (DMSO-d_6, δ): 1.38 (9H, s), 3.59 (3H, s), 5.05 (1H, d, J=7.9 Hz), 6.70 (2H, d, J=8.5 Hz), 7.16 (2H, d, J=8.5 Hz), 7.60 (1H, d, J=7.9 Hz), 9.48 (1H, s)

Preparation 3

To a suspension of N-(t-butoxycarbonyl)-D-2-(p-hydroxyphenyl)glycine methyl ester (6.8 g) and potassium bicarbonate (1.84 g) in N,N-dimethylformamide (34 ml) was added octyl bromide (4.176 ml). The mixture was stirred for 6 hours at 60° C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was separated and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give N-(t-butoxycarbonyl)-D-2-(p-octyloxyphenyl)glycine methyl ester (6.96 g).

IR (Nujol): 1710, 1490, 1240, 1160 cm^{-1}

NMR (DMSO-d_6, δ): 0.859 (3H, t, J=6.2 Hz), 1.17–1.33 (10H, m), 1.38 (9H, s), 1.60–1.80 (2H, m), 3.59 (3H, s), 3.93 (2H, t, J=6.3 Hz), 5.11 (1H, d, J=7.9 Hz), 6.87 (2H, d, J=8.7 Hz), 7.27 (2H, d, J=8.7 Hz), 7.68 (1H, d, J=7.9 Hz)

Preparation 4

To 4N aqueous solution of sodium hydroxide (8.77 ml) was added N-(t-butoxycarbonyl)-D-2-(p-octyloxyphenyl)glycine methyl ester (6.9 g) and stirred for 1.5 hours at room temperature. The reaction mixture was added to a mixture of water and ethyl acetate and 1N hydrochloric acid was added thereto to adjust the mixture to pH 3. The organic layer was separated and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give N-(t-butoxycarbonyl)-D-2-(p-octyloxyphenyl)glycine (3.9 g).

NMR (DMSO-d_6, δ): 0.860 (3H, t, J=6.8 Hz), 1.17–1.33 (10H, m), 1.38 (9H, s), 1.60–1.80 (2H, m), 3.93 (2H, t, J=6.4 Hz), 5.10 (1H, d, J=8.2 Hz), 6.87 (2H, d, J=8.7 Hz), 7.28 (2H, d, J=8.7 Hz), 7.46 (1H, d, J=8.2 Hz)

Preparation 5

To a solution of N-(t-butoxycarbonyl)-D-2-(p-octyloxyphenyl)glycine (1 g) in acetonitrile (10 ml) and pyridine (0.213 ml) in acetonitrile (10 ml) was added N,N'-disuccinimidyl carbonate (0.675 g). The mixture was stirred for 12 hours at room temperature. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was separated and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give N-(t-butoxycarbonyl)-D-2-(p-octyloxyphenyl)glycine succinimido ester (0.92 g).

IR (Nujol): 3350, 1810, 1730, 1680 cm^{-1}

NMR (DMSO-d_6, δ): 0.862 (3H, t, J=6.7 Hz), 1.17–1.33 (10H, m), 1.40 (9H, s), 1.60–1.80 (2H, m), 2.77 (4H, s), 3.97 (2H, t, J=6.5 Hz), 5.54 (1H, d, J=8.1 Hz), 6.91 (2H, d, J=8.7 Hz), 7.39 (2H, d, J=8.7 Hz), 8.05 (1H, d, J=8.1 Hz)

Preparation 6

N-(t-Butoxycarbonyl)-L-tyrosine methyl ester was obtained according to a similar manner to that of Preparation 2.

IR (Nujol): 3430, 3360, 1730, 1670, 1170 cm^{-1}

NMR (DMSO-d_6, δ): 1.33 (9H, s), 2.90 (2H, m), 3.59 (3H, s), 4.05 (1H, m), 6.65 (2H, d, J=8.4 Hz), 7.00 (2H, d, J=8.4 Hz), 7.21 (1H, d, J=8.0 Hz), 9.22 (1H, s)

Preparation 7

O^4-Octyl-N-(t-butoxycarbonyl)-L-tyrosine methyl ester was obtained according to a similar manner to that of Preparation 3.

IR (Nujol): 3350, 1735, 1685, 1250, 1170 cm^{-1}

NMR (DMSO-d_6, δ): 0.859 (3H, t, J=6.7 Hz), 1.20–1.30 (10H, m), 1.68 (2H, quintet, J=7.3 Hz), 2.82 (2H, m), 3.60 (3H, s), 3.91 (2H, t, J=7.3 Hz), 4.08 (1H, m), 6.81 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=8.6 Hz), 7.25 (1H , d, J=8.0 Hz)

Preparation 8

O^4-Octyl-N-(t-butoxycarbonyl)-L-tyrosine was obtained according to a similar manner to that of Preparation 4.

IR (Nujol): 3400–2900 (br), 1700, 1240, 1160 cm^{-1}

NMR (DMSO-d_6, δ): 0.859 (3H, t, J=6.8 Hz), 1.20–1.30 (10H, m), 1.32 (9H, s), 1.68 (2H, quintet, J=7.0 Hz), 2.67–2.95 (1H, m), 3.90 (2H, t, J=7.0 Hz), 4.01 (1H, m), 6.81 (2H, d, J=8.6 Hz), 7.02 (1H, d, J=8.3 Hz), 7.13 (2H, d, J=8.6 Hz)

Preparation 9

O^4-Octyl-N-(t-butoxycarbonyl)-L-tyrosine succinimido ester was obtained according to a similar manner to that of Preparation 5.

IR (Nujol): 3350, 1780, 1720, 1690 cm^{-1}

NMR (DMSO-d_6, δ): 0.860 (3H, t, J=6.7 Hz), 1.20–1.30 (10H, m), 1.32 (9H, s), 1.68 (2H, quintet, J=7.0 Hz), 2.82 (4H, s), 2.80–3.20 (1H, m), 3.92 (2H, t, J=7.0 Hz), 4.44 (1H, m), 6.81 (2H, d, J=8.5 Hz), 7.22 (2H, d, J=8.5 Hz), 7.60 (1H, d, J=8.3 Hz)

Preparation 10

(1) A seed medium (160 ml) consisting of sucrose 4%, cotton seed flour 2%, dried yeast 1%, peptone 1%, KH_2PO_4 0.2%, $CaCO_3$ 0.2% and Tween 80 (made by NAKARAI CHEMICALS LTD.) 0.1% was poured into each of two 500 ml Erlenmeyer flasks and sterilized at 121° C. for 30 minutes. A loopful of slant culture of Coleophoma sp. F-11899 was inoculated to each of the medium and cultured under shaking condition at 25° C. for 4 days.

A production medium (20 liters) consisting of Pine Dex #3 (made by Matsutani Chemical Ltd.) 3%, glucose 1%, wheat germ 1%, cotton seed flour 0.5%, KH_2PO_4 2%, $Na_2HPO_4.12H_2O$ 1.5%, $ZnSO_4.7H_2O$ 0.001% and Adekanol (defoaming agent, made by Asahi Denka Co., Ltd.) 0.05% was poured into a 30 liter-jar fermentor and sterilized at 121° C. for 30 minutes.

The resultant seed culture broth (320 ml) was inoculated to the production medium and cultured at 25° C. for 4 days, agitated at 200 rpm and aerated at 20 liters per minute. To the cultured broth thus obtained (20 liters) was added an equal volume of acetone. After occasionally stirring at room temperature for a while, the broth was filtered. The filtrate was concentrated in vacuo to remove acetone. The aqueous filtrate (10 liters) was washed with two equal volume of ethyl acetate and extracted with n-butanol (10 liters) twice. The combined n-butanol layer was concentrated in vacuo and the residue was applied on a column (300 ml) of Silica gel 60 (made by E. Merck) and eluted with a stepwise organic solvent mixture consisting of dichloromethane-methanol. The fractions having anti-Candida activity were eluted in the range of the solvent mixture (3:1 through 1:1). The active fractions were combined and concentrated in vacuo to dryness. The residue was dissolved in 50% aqueous methanol (15 ml) and applied on a column (250 ml) of ODS YMC GEL (made by Yamamura Chemical Lab.). The column was washed with 50% aqueous methanol and eluted with 80% aqueous methanol. The eluate was concentrated and was further purified on a centrifugal partition chromatography (CPC) using a solvent system n-butanol:methanol:water (4:1:5) of upper stationary phase and lower mobile phase in a descending mode. The pooled fractions containing the object compound (major component) were concentrated in vacuo and applied on a column (35 ml) of silica gel 60. The column was developed with n-butanol:acetic acid:water (6:1:1). The active fractions were combined and concentrated in vacuo to dryness and dissolved in a small volume of 50% aqueous methanol. The solution was passed through a column (3.5 ml) of ODS YMC GEL. The column was washed with 50% aqueous methanol and eluted with methanol. The eluate was concentrated to dryness, dissolved in a small volume of water and adjusted to pH 7.0 with 0.01N NaOH. The solution was freeze-dried to give a white powder of said compound in its sodium salt form (hereinafter referred to as FR901379 substance (SEQ ID NO: 1)) (11 mg).

The FR901379 substance (SEQ ID NO: 1) as obtained has the following physico-chemical properties.

Appearance:
white powder

Nature:
neutral substance

Melting point:
215°–221° C. (dec.)

Specific rotation:
$[\alpha]_D^{23}$ −20.3 (C: 0.5, H_2O)

Molecular formula:
$C_{51}H_{81}N_8O_{21}SNa$

Elemental Analysis:
Calcd.: for $C_{51}H_{81}N_8SO_{21}Na$ C 51.17, H 6.77, N 9.36, S 2.68 (%) Found: C 49.61, H 7.58, N 7.65, S 2.14 (%)

Molecular weight:
HRFAB-MS: 1219.5078 (Calcd for $C_{51}H_{82}N_8SO_{21}+2Na-H$: 1219.5032)

Solubility:
soluble: methanol, water
slightly soluble: ethyl acetate, acetone
insoluble: chloroform, n-hexane

Color reaction:
positive: iodine vapor reaction, cerium sulfate reaction, ferric chloride reaction, Ninhydrin reaction
negative: Dragendorff reaction, Ehrlich reaction

Thin layer chromatography (TLC):

Stationary phase	Developing solvent	Rf value
silica gel*	n-butanol:acetic acid; water (3:1:1)	0.36
	ethyl acetate:isopropyl alcohol:water (5:3:1)	0.31

*Silica Gel 60 (made by E. Merck)

Ultraviolet absorption spectrum:
$\lambda_{max}^{methanol}$ ($E_{1\ cm}^{1\%}$): 207(169), 276(13.5), 225(sh),283(sh) nm
$\lambda_{max}^{methanol+0.01N\text{-}NaOH}$ ($E_{1\ cm}^{1\%}$): 209(232), 244(59.5), 284(13.5), 294(sh) nm

Infrared absorption spectrum:

phenyl(lower)alkoxy(lower)alkanoyl which may have 1 to 3 higher alkoxy; or

phenylamino(lower)alkanoyl which may have 1 to 3 higher alkoxy.

11. A compound of claim 1, wherein

R^1 is benzoyl substituted with piperazinyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy(higher)alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, cyclo(lower)alkyl having phenyl, phenyl having cyclo(lower)alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl,

in which benzoyl may have halogen;

benzoyl substituted with isoxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy(higher)alkoxy, and phenyl substituted with phenyl having lower alkoxy;

benzoyl substituted with phenyl having lower alkoxy(higher)alkoxy;

benzoyl substituted with phenyl having lower alkyl;

benzoyl substituted with phenyl having higher alkyl;

phenyl(lower)alkenoyl substituted with phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, lower alkyl, higher alkyl, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy, halo(higher)alkoxy and lower alkoxy(higher)alkoxy;

benzoyl substituted with thiadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo(lower)alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo(lower)alkyl, phenyl having piperidyl, and phenyl having lower alkoxy(higher)alkoxy; or

benzoyl substituted with oxadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy(higher)alkoxy, higher alkyl and phenyl substituted with phenyl having lower alkoxy.

12. A compound of claim 11, wherein

R^1 is benzoyl substituted with phenyl having lower alkoxy(higher)alkoxy; or

benzoyl substituted with phenyl having lower alkyl.

13. A compound of claim 11, wherein

R^1 is benzoyl substituted with piperazinyl which may have phenyl having lower alkoxy;

benzoyl substituted with isoxazolyl which may have phenyl having lower alkoxy;

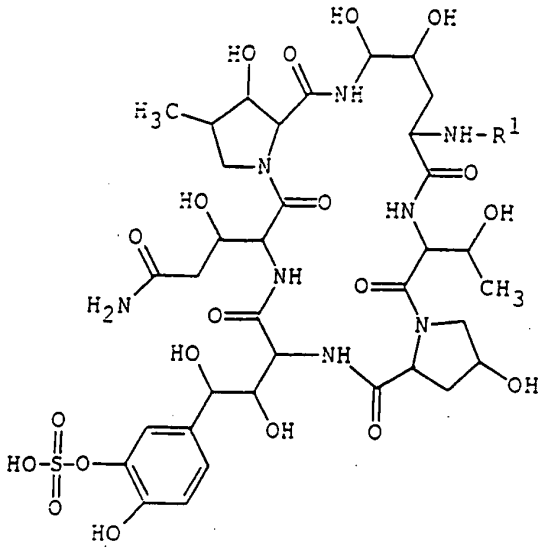
benzoyl substituted with thiadiazolyl which may have phenyl having lower alkoxy(higher)alkoxy; or

benzoyl substituted with oxadiazolyl which may have phenyl having lower alkoxy.

14. A compound of claim 11, wherein

R^1 is phenyl(lower)alkenoyl substituted with phenyl which may have lower alkoxy.

15. A process for the preparation of a polypeptide compound of the formula [I] :



[I]

wherein

R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with 1,2,3,4-tetrahydro-isoquinoline having higher alkoxy;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy;

ar(C_2-C_6)alkanoyl substituted with aryl having one or more suitable substituent(s), in which ar(C_2-C_6)alkanoyl may have one or more suitable substituent(s);

aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s);

aroyl substituted with aryl having heterocyclic(higher)alkoxy, in which heterocyclic group may have one or more suitable substituent(s);

aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkenyl(lower)alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl;

aryloxy(lower)alkanoyl which may have one or more suitable substituent(s);

ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s);

arylamino(lower)alkanoyl which may have one or more suitable substituent(s);

lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy;

lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have one or more suitable substituent(s);

aroyl substituted with aryl having heterocyclicoxy, in which heterocyclicoxy may have one or more suitable substituent(s);

aroyl substituted with cyclo(lower)alkyl having lower alkyl;

indolylcarbonyl having higher alkyl;

naphthoyl having lower alkyl;

naphthoyl having higher alkyl;

naphthoyl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower)alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl which has aryl having lower alkoxy;

aroyl substituted with aryl which has aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl having heterocyclicoxy(higher)alkoxy;

aroyl substituted with aryl having aryloxy(lower)alkoxy;

aroyl substituted with aryl having heterocycliccarbonyl(higher)alkoxy;

lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy;

lower alkanoyl substituted with furyl which has aryl substituted with aryl having lower alkoxy;

lower alkanoyl substituted with triazolyl which

has oxo and aryl having higher alkyl;

higher alkanoyl having hydroxy;

higher alkanoyl having ar(lower)alkyl and hydroxy;

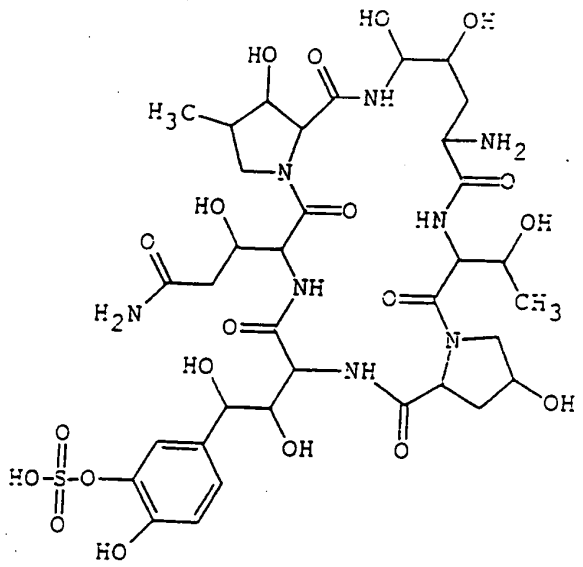
3-methyl-tridecenoyl; or

(C_2-C_6)alkanoyl substituted with aryl having higher alkoxy, in which (C_2-C_6)alkanoyl may have amino or protected amino, and

a pharmaceutically acceptable salt thereof,

which comprises

1) reacting a compound of the formula :



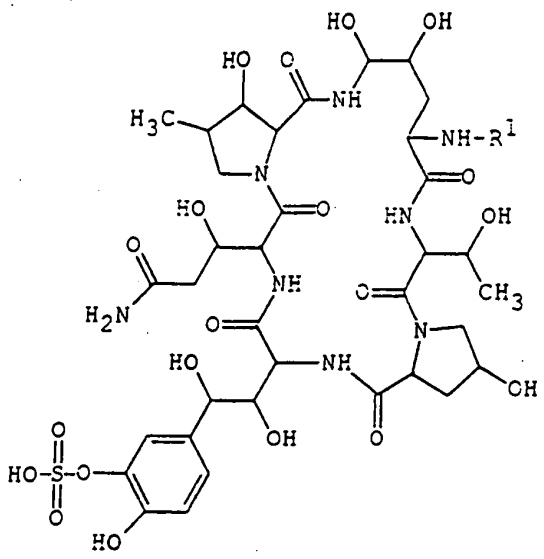
[II]

or its reactive derivative at the amino group or a salt thereof, with a compound of the formula :

$$R^1 - OH \qquad [III]$$

wherein R^1 is defined above,

or its reactive derivative at the carboxy group or a salt thereof, to give a compound [I] of the formula :



[I]

wherein R^1 is defined above,

or a salt thereof.

16. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

17. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

18. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

19. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/809,729	05/21/97	OHKI H	18-971-0-PCT

EXAMINER

18M1/0828

OBLON SPIVAK MCCLELLAND
MAIER AND NEUSTADT
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON VA 22202

ART UNIT	PAPER NUMBER
1811	5

DATE MAILED: 08/28/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

RD 11-28-97

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-17 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings. filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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AUG 29 1997
OBLON, SPIVAK, McCLELLAND
MAIER & NEUSTADT, P.C.

EXAMINER'S ACTION

1. Claims 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 provides for the use of a compound or a salt thereof as a medicament, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 17 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)

Claim 18 is a duplicate of claim 1 because claim 18 has no further structural limitation that would distinguish the compounds recited in claim 18 from those recited in claim 1.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toshiro et al (EPA 0462531) or Toshrio et al (USP 5,376634).

The present invention relates to compounds that have the generally formula set forth on pages 2-5 of the specification. The instant compounds have antimicrobial activity. Additionally, the invention also relates to a process of making said compounds.

Toshiro et al (EPA 0462531) teaches antimicrobial compounds which read on the compound of the present invention, especially when R1 is acyl, R2 is hydroxyl, and R3 is hydrosulfonyloxy, and R4 is carbamoyl provided that R1 is not palimitoyl . The compounds of the present invention fall with the scope of the invention taught by Toshiro et al. Therefore it would be obvious to one of ordinary skill in the art to preferentially selective the appropriate radicals needed to prepare the compounds of the present invention. Furthermore it would be within the skill of the art and therefore obvious to use the process taught by Toshiro et al to prepare the peptides of the instant invention, wherein the compounds have antimicrobial activity.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 5,374634. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention are co-extensive. Essentially, the present invention relates to compounds, pharmaceutical compositions, and a methods of making compounds set forth on pages 2-5 of the specification. The compounds of the instant invention fall within the scope of the invention taught by Toshiro et al; therefore it is within the skill of the art to preferentially select the appropriate radicals for preparing the compounds of the invention, wherein the compounds have antimicrobial activity.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applicants Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Marshall whose telephone number is (703) 308-1030.

Sgm
August 26, 1997

CECILIA J. TSANG
SUPERVISORY PATENT EXAMINER
GROUP 1800

NOTICE TO COMPLY WITH R JIREMENTS FOR PATENT APPLI TIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application dc not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☑ 1. This application clearly fails to comply with the requirements of 37 CFR 1 2) - 1.825. Applicant's attention is directed to these regulations, published at 1114 C May 15, 1990 and at 55 FR 18230, May 1, 1990.

☑ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☑ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitt However, the content of the computer readable form does not comply with the requireme of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has be found to be damaged and/or unreadable as indicated on the attached CRF Diskette Probl Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☑ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☑ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☑ A statement that the content of the paper and computer readable copies are the and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please cont

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

NOTICE OF REFERENCES CITED

SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER	
08/809723	1811		5

APPLICANT(S)

OHKI ET AL

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	5376634	12/27/94	Iwamoto et al	530	317	
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
*	L	0462531	12/27/91	EP					
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R

S

T

U

EXAMINER	DATE
SANDRA MARSHALL	8-26-97

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

substituted with phenyl having lower alkoxy, phenyl having heterocyclic group and oxo, in which aroyl may have halogen;

aroyl substituted with aryl having heterocyclic(higher)alkoxy, in which heterocyclic group may have lower alkyl;

aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkenyl(lower)alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower alkyl; or

aroyl substituted with aryl having higher alkyl.

5. A compound of claim 1, wherein

R^1 is aryloxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

ar(lower)alkoxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl

having lower alkyl, and oxo; or

arylamino(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

6. A compound of claim 1, wherein

R^1 is lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy;

lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have amino or protected amino;

aroyl substituted with aryl having heterocyclicoxy, in which heterocyclicoxy may have phenyl;

aroyl substituted with cyclo(lower)alkyl having lower alkyl;

indolylcarbonyl having higher alkyl;

naphthoyl having lower alkyl;

naphthoyl having higher alkyl;

naphthoyl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower)alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl which has phenyl having lower alkoxy;

aroyl substituted with aryl which has phenyl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl having

heterocyclicoxy(higher)alkoxy;

aroyl substituted with aryl having phenoxy(lower)alkoxy;

aroyl substituted with aryl having heterocycliccarbonyl(higher)alkoxy;

lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy;

lower alkanoyl substituted with furyl which has aryl substituted with phenyl having lower alkoxy;

lower alkanoyl substituted with triazolyl which has oxo and phenyl having higher alkyl;

higher alkanoyl having hydroxy;

higher alkanoyl having benzyl and hydroxy;

3-methyl-tridecenoyl; or

(C_2-C_6)alkanoyl substituted with aryl having higher alkoxy, in which (C_2-C_6)alkanoyl may have amino or protected amino.

7. A compound of claim 2, wherein

R^1 is lower alkanoyl substituted with pyridyl or pyridazinyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of higher alkoxy, higher alkoxy(lower)alkyl, phenyl having higher alkoxy, phenyl substituted with phenyl having lower alkoxy, piperazinyl substituted with phenyl having higher alkoxy, piperazinyl substituted with phenyl having lower alkoxy(higher)alkoxy, and piperazinyl substituted with phenyl having lower alkoxy;

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline having higher alkoxy and lower alkoxy carbonyl;

lower alkanoyl substituted with coumarin which may have 1 to 3 substituent(s) selected from the group consisting of higher alkoxy, and oxo;

lower alkanoyl substituted with benzothiophenyl which may have 1 to 3 higher alkoxy;

lower alkanoyl substituted with benzo[b]furanyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkoxy and lower alkyl;

lower alkanoyl substituted with benzooxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl substituted with phenyl having lower alkyl, and pyridyl having higher alkoxy;

lower alkanoyl substituted with benzimidazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, and phenyl having lower alkoxy; or

lower alkanoyl substituted with piperidyl or piperazinyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having higher alkoxy, and naphthoyl having higher alkoxy.

8. A compound of claim 3, wherein

R^1 is phenyl(lower)alkenoyl substituted with phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, lower alkyl, higher alkyl, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy, halo(higher)alkoxy, and lower alkoxy(higher)alkoxy;

naphthyl(lower)alkenoyl which may have 1 to 3 higher alkoxy;

lower alkynoyl which may have 1 to 3 substituent(s) selected from the group consisting of naphthyl having higher alkoxy, and phenyl

substituted with phenyl having lower alkyl;

phenyl(C_2-C_6)alkanoyl substituted with phenyl which has 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, and phenyl having lower alkoxy(lower)alkyl,

in which phenyl(C_2-C_6)alkanoyl may have hydroxy, oxo, protected amino or amino; or

(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy.

9. A compound of claim 4, wherein

R^1 is benzoyl substituted with saturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy(higher)alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, piperidyl, cyclo(lower)alkyl having phenyl, phenyl having cyclo(lower)alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl,

in which benzoyl may have halogen;

benzoyl substituted with unsaturated 5-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy(higher)alkoxy, and phenyl substituted with phenyl having lower alkoxy;

benzoyl substituted with 5 or 6-membered heteromonoccyclic group containing 1 or 2 nitrogen

atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl and phenyl having lower alkoxy;

benzoyl substituted with 5-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and 1 to 2 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo(lower)alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo(lower)alkyl, phenyl having piperidine, and phenyl having lower alkoxy(higher)alkoxy;

benzoyl substituted with phenyl having higher alkoxy substituted with unsaturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom;

benzoyl substituted with phenyl having higher alkoxy substituted with saturated 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have lower alkyl;

benzoyl substituted with phenyl having lower alkoxy(higher)alkoxy;

benzoyl substituted with phenyl having lower alkenyl(lower)alkoxy;

benzoyl substituted with 2 lower alkoxy;

benzoyl substituted with phenyl having lower alkyl; or

benzoyl substituted with phenyl having higher alkyl.

10. A compound of claim 5, wherein

R^1 is phenyloxy(lower)alkanoyl which may have 1 to 3 higher alkoxy;

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,107,458

DATED : August 22, 2000

INVENTOR(S): Hidenori OHKI et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page, item [30], the Foreign Application Priority Data is erroneously listed. It should be:

--[30] Foreign Application Priority Data

Oct. 7, 1994 [GB] United Kingdom.....9420425
Apr. 28, 1995 [GB] United Kingdom.....9508745--

Signed and Sealed this

Twenty-ninth Day of May, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office

Dept.: CHEMICAL

OSMM&N File No. 18-971-0 PCT By: SGB:VKS:mab

Patent No. 6,107,458

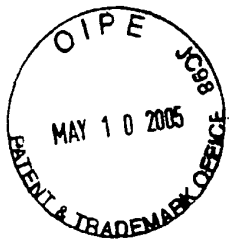
In the matter of the Patent of: Hidenori OHKI et al

For: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

Due Date: N/A

The following has been received in the U.S. Patent Office on the date stamped hereon:

- Credit Card Form for $100.00
- Deposit Account Order Form
- PTO Cover Letter
- Request for Certificate of Correction
- Certificate of Correction (in duplicate, 3 pp.)
- Photocopy of Original Claims of Specification as Filed 05/21/97
- Photocopy of Office Action Mailed 08/28/97
- Photocopy of U.S. 5,376,634
- Photocopy of Office Action Mailed 06/15/98
- Photocopy of Amendment Pursuant to 37 C.F.R. §1.116 Filed 12/07/98
- Photocopy of Preliminary Amendment Filed 02/08/99



COPY

OBLON
SPIVAK
MCCLELLAND
MAIER
&
NEUSTADT
P.C.

ATTORNEYS AT LAW

STEPHEN G. BAXTER
(703) 413-3000
SBAXTER@OBLON.COM

DOCKET NO.: 18-971-0 PCT

DIRECTOR OF THE UNITED STATES
PATENT AND TRADEMARK OFFICE
ALEXANDRIA, VIRGINIA 22313

RE: Patent No.: 6,107,458
Serial No.: 08/809,723
Patentees: Hidenori OHKI et al
Issue Date: August 22, 2000
For: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

SIR:

Attached hereto for filing are the following papers:

REQUEST FOR CERTIFICATE OF CORRECTION; CERTIFICATE OF CORRECTION (IN DUPLICATE, 3 PP.); PHOTOCOPY OF ORIGINAL CLAIMS OF SPECIFICATION AS FILED 05/21/97; PHOTOCOPY OF OFFICE ACTION MAILED 08/28/97; PHOTOCOPY OF U.S. 5,376,634; PHOTOCOPY OF OFFICE ACTION MAILED 06/15/98; PHOTOCOPY OF AMENDMENT PURSUANT TO 37 C.F.R. §1.116 FILED 12/07/98; PHOTOCOPY OF PRELIMINARY AMENDMENT FILED 02/08/99

Our credit card payment form in the amount of $100.00 is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R §1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. §1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Stephen G. Baxter
Attorney of Record
Registration No. 32884

COPY

Customer Number
22850
(703) 413-3000 (phone)
(703) 413-2220 (fax)

DOCKET NO.: 18-971-0 PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PATENT OF: :
Hidenori OHKI et al :

PATENT NO.: 6,107,458 :

ISSUED: August 22, 2000 :

FOR: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

COPY

REQUEST FOR CERTIFICATE OF CORRECTION

DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE
ALEXANDRIA, VA 22313-

SIR:

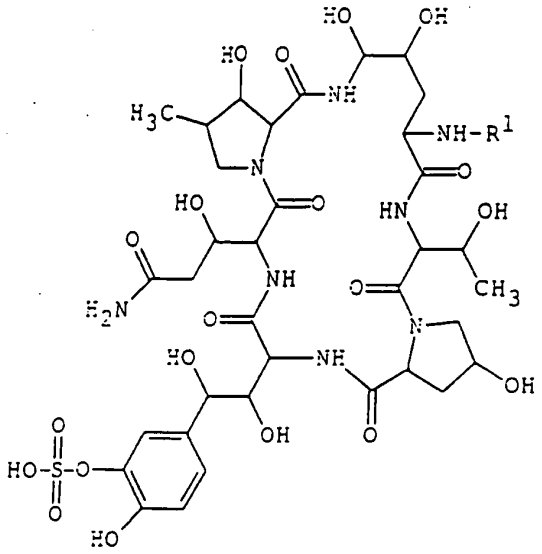
The following is a request for a Certificate of Correction in U.S. Patent Application Serial Number 08/809,723, now U.S. Patent Number 6,107,458.

REMARKS

A Certificate of Correction under 35 U.S.C. §255 is respectfully requested, in U.S. Patent Number 6,107,458 ("the '458 patent"). The facts are as follows.

The '458 patent issued from U.S. Patent Application Serial Number 08/809,723 ("the '723 application"), which was a 371 application of PCT/JP95/01983, filed on September 29, 1995. The '723 application entered the national stage in the U.S. on April 27, 1997, and the requirements of 35 U.S.C. § 371 were completed on May 21, 1997.

The '723 application was filed with 19 original claims, a copy of which is attached hereto at Tab 1. Notably, as shown by the formula [I] in Claim 1, the '723 application is directed toward certain cyclic hexapeptides. For convenience, formula [I] is repeated below:

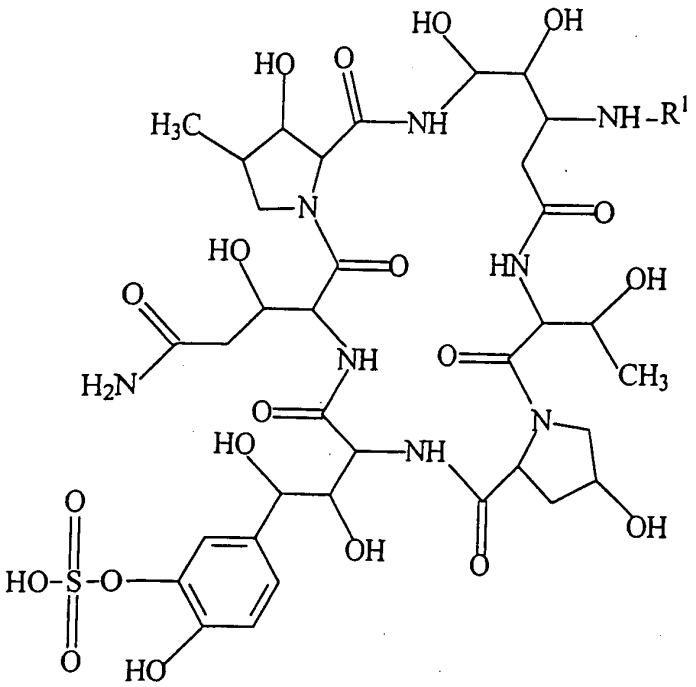


[I]

It is also noted that the structure of formula [I] in originally presented Claim 1 is fully supported by the specification of both the '723 application, as originally filed, and the '458 patent, as issued. In support of this assertion, Applicants cite page 2 of the '723 application, as originally filed, and col. 1 of the '458 patent.

In the Office Action dated August 28, 1997, Claims 1-19 were rejected under 35 U.S.C. § 103(a) in view of, *inter alia*, U.S. Patent No. 5,376,634 (Iwamoto et al.). For convenience, copies of the Office Action dated August 28, 1997, and Iwamoto et al. are attached hereto at Tabs 2 and 3. In the Request for Reconsideration filed on March 2, 1998, no amendments were made to the claims other than the cancellation of Claims 17 and 18.

In the Office Action dated June 5, 1998, Claims 1-16 were finally rejected in view of Iwamoto et al. (copy attached hereto at Tab 4). In response, Applicants canceled Claims 1-16 and added new Claims 20-36 (*see*, copy of the Amendment Pursuant to 37 C.F.R. §1.116, filed on December 7, 1998, a copy of which is attached hereto at Tab 5). However, a typographical error was introduced into the structure for formula [I] in Claims 20, 23, 28, 29, and 30 and the structure for formula [II] in Claims 29 and 30. Specifically, the position of the attachment of the $-NH-R^1$ group was inadvertently moved by one position on the main ring as shown below:



[I]

Inspection of the remarks, which accompanied the Amendment, makes it clear that the shift of the position of the attachment of the $-NH-R^1$ group on the main ring was merely an inadvertent typographical error. Specifically, there is nothing in the remarks which accompanied the Amendment which would in anyway indicated that this shift in position was intentional.

In the Advisory Action dated December 21, 1998, the Examiner indicated that the amendment filed on December 7, 1998, would not be entered. Applicants then re-filed the '723 application as a CPA along with a Preliminary Amendment in which Claims 20-36 were replaced with Claims 37-41 (*see*, copy of the Preliminary Amendment, filed on February 8, 1999, a copy of which is attached hereto at Tab 6). However, the typographical error in the structure of formula [I] (and in the structure of formula [II]) which was introduced in the Amendment filed on December 7, 1998, was propagated in the Preliminary Amendment filed on February 8, 1999.

Once again, inspection of the remarks which accompanied the Preliminary Amendment filed on February 8, 1999, shows that the shift of the position of the attachment of the $-NH-R^1$ group on the main ring was merely a propagation of the inadvertent typographical error which had been previously introduced. Moreover, the fact that the Examiner then allowed the application

indicates that this typographical error simply went unnoticed and that the Examiner had intended to allow those claims with the correct structure.

In other words, the entire prosecution history points to the conclusion that the mistake in the structure of formulae [I] and [II] is simply a typographical error which went unnoticed during prosecution. Further, there is no evidence that this error was introduced in bad faith.

As stated in 35 U.S.C. § 255:

> Whenever a mistake of a clerical or ***typographical*** nature, or of a minor character, which was not the fault of the Patent and Trademark Office, appears in a patent and a showing has been made that such mistake occurred in ***good faith***, the Director may upon payment of the required fee, issue a certificate of correction, if the correction does not involve such changes in the patent as would constitute ***new matter*** or would require ***re-examination***.

As can be seen from the facts set out above, this particular instance meets all the requirements for the issuance of a certificate of correction. Specifically, the error in the structure of formulae [I] and [II]:

(1) is a typographical error; and

(2) occurred in good faith.

Moreover, correction of the error in the structure of formulae [I] and [II]:

(3) would not introduce any new matter; and

(4) would not require re-examination.

In the Certificate of Correction filed herewith, only the correction of the structure of formulae [I] and [II] to that which was originally filed is sought. Since the specification as filed contained the correct structure, correction of the structure of formulae [I] and [II] would clearly not introduce any new matter. Further, since it is clear from the prosecution history that the error in the structure of formulae [I] and [II] simply went unnoticed during the prosecution and that both the Applicant and the Examiner both thought that the allowed claims contained the correct structure, the requested correction would just as clearly not require re-examination.

For these reasons, it is respectfully requested that the Certificate of Correction filed herewith be granted and issued.

Since all errors are the fault of the Patentee, a credit card payment form for $100.00 is being submitted herewith. 35 U.S.C. § 255 and 37 C.F.R. § 1.323. The requested corrections are attached on Form PTO 1050.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

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Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220

Stephen G. Baxter
Attorney of Record
Registration No. 32,884

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,170,458

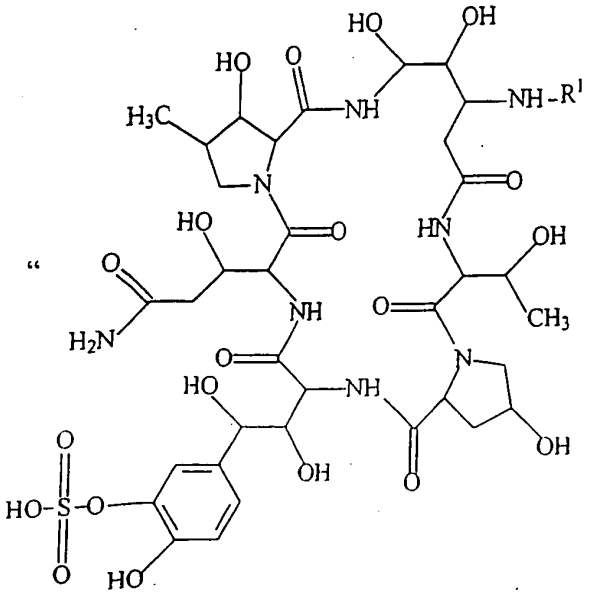
DATED: August 22, 2000

INVENTOR(S): Hidenori OHKI et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 137, lines 34-54, Claim 1, formula (I):

"

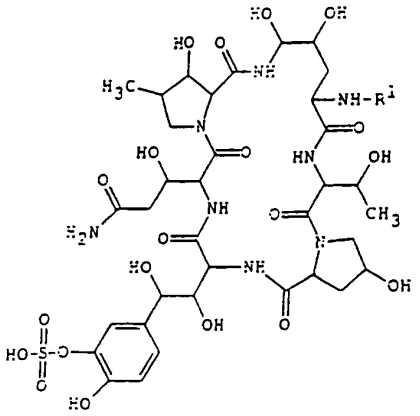


[I]

"

should read:

--



[I]

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

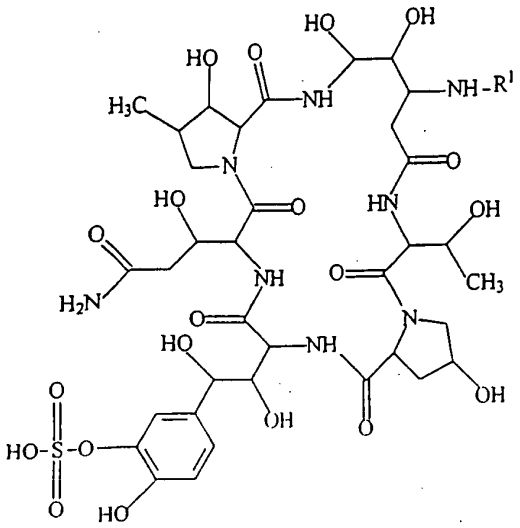
PATENT NO. : 6,170,458

DATED: August 22, 2000

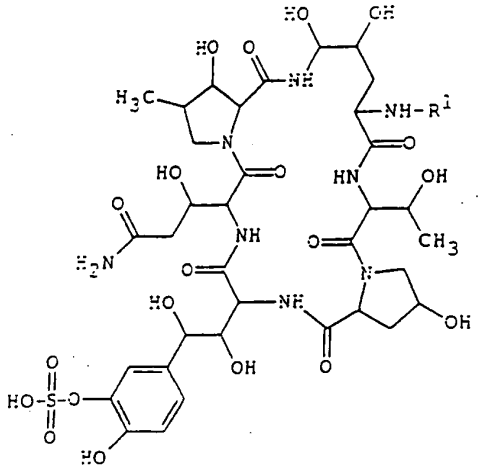
INVENTOR(S): Hidenori OHKI et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 138, lines 1-23, Claim 3, formula (I):

"  [I] "

should read

--  [I] --

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Patent No. 6,107,458

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

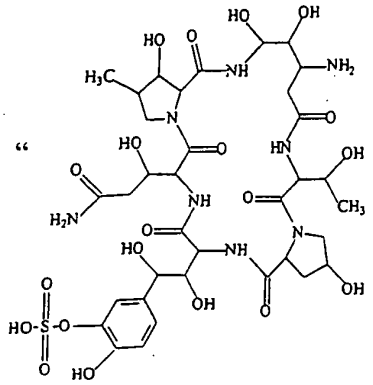
PATENT NO. : 6,170,458

DATED: August 22, 2000

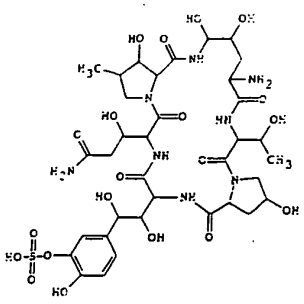
INVENTOR(S): Hidenori OHKI et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 138, lines 28-49, Claim 3, formula (II):

"  (II) "

should read:

--  (II) --

COPY

Patent No. 6,107,458

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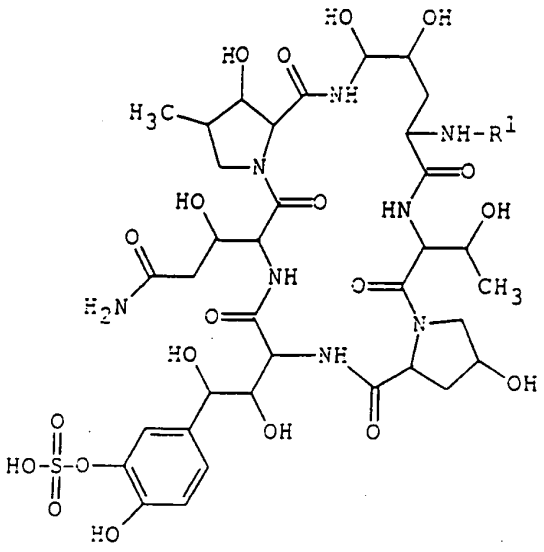
CLAIMS

1. A polypeptide compound of the following general formula :



[I]

wherein R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s)

which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8 membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy;

ar(C_2-C_6)alkanoyl substituted with aryl having one or more suitable substituent(s), in which ar(C_2-C_6)-alkanoyl may have one or more suitable substituent(s);

aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s);

aroyl substituted with aryl having heterocyclic(higher)alkoxy, in which heterocyclic group may have one or more suitable substituent(s);

aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkenyl(lower)alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl;

aryloxy(lower)alkanoyl which may have one or more suitable substituent(s);

ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s);

arylamino(lower)alkanoyl which may have one or more suitable substituent(s);

lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy;

lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have one or more suitable substituent(s);

aroyl substituted with aryl having heterocyclicoxy, in which heterocyclicoxy may have one or more suitable substituent(s);

aroyl substituted with cyclo(lower)alkyl having lower alkyl;

indolylcarbonyl having higher alkyl;

naphthoyl having lower alkyl;

naphthoyl having higher alkyl;

naphthoyl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower)alkoxy(higher)-alkoxy;

aroyl substituted with aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl which has aryl having lower alkoxy;

aroyl substituted with aryl which has aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl having heterocyclicoxy(higher)alkoxy;

aroyl substituted with aryl having aryloxy(lower)alkoxy;

aroyl substituted with aryl having heterocyclic carbonyl(higher)alkoxy;

lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy;

lower alkanoyl substituted with furyl which has aryl substituted with aryl having lower alkoxy;

lower alkanoyl substituted with triazolyl which has oxo and aryl having higher alkyl;

higher alkanoyl having hydroxy;

higher alkanoyl having ar(lower)alkyl and hydroxy;

3-methyl-tridecenoyl; or

(C_2-C_6)alkanoyl substituted with aryl having higher alkoxy, in which (C_2-C_6)-alkanoyl may have amino or protected amino, and

a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having higher alkoxy, phenyl substituted with phenyl having lower alkoxy, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having lower alkoxy(higher)alkoxy, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having lower alkoxy, and oxo;

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline having higher alkoxy and lower alkoxy carbonyl;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy,

naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have higher alkoxy, and oxo;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atoms which may have 1 to 3 substituent(s) selected from the group containing of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo; or

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3

substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

3. A compound of claim 1, wherein

R^1 is ar(lower)alkenoyl substituted with aryl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy, halo(higher)alkoxy, lower alkoxy(higher)alkoxy, and oxo;

naphthyl(lower)alkenoyl which may have 1 to 3 higher alkoxy;

lower alkynoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having

lower alkyl, and oxo;

ar(C_2-C_6)alkanoyl substituted with aryl having 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy(lower)alkoxy, and oxo, in which ar(C_2-C_6)-alkanoyl may have hydroxy, oxo, protected amino or amino; or

(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy.

4. A compound of claim 1, wherein

R^1 is aroyl substituted with heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy(higher)alkoxy, phenyl having higher alkenyloxy, heterocyclic group substituted with phenyl having lower alkoxy, heterocyclic group, cyclo(lower)alkyl having phenyl, phenyl having cyclo(lower)alkyl, phenyl substituted with heterocyclic group having lower alkyl and oxo, cyclo(lower)alkyl having lower alkyl, phenyl

evaporated under reduced pressure to give 4-Octyloxyphenylsuccinimidyl carbonate (0.59 g).

IR (KBr): 2927, 1876, 1832, 1735 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.3Hz), 1.2–1.55 (10H, m), 1.67–1.87 (2H, m), 2.87 (4H, s), 3.94 (2H, t, J=6.5Hz), 6.89 (2H, d, J=9.2Hz), 7.17 (2H, d, J=9.2Hz)

APCI-MASS: m/z=364 (M^++1)

The following compounds (Preparations 75 to 88) were obtained according to a similar manner to that of Preparation 1.

Preparation 75

Methyl 4-[4-(6-phenylpyridazin-3-yl-oxy)phenyl] benzoate

IR (KBr): 1708, 1427, 1280, 1197, 1112 cm^{-1}

NMR ($CDCl_3$, δ): 3.95 (3H, s), 7.2–7.7 (10H, m), 7.92 (1H, d, J=9.2Hz), 8.0–8.2 (4H, m)

APCI-MASS: m/z=383 $(M+H)^+$

Preparation 76

Methyl 4-[4-(5-bromopentyloxy)phenyl]benzoate

IR (KBr): 2946, 2871, 1716, 1602, 1294, 1199, 1112, 837 cm^{-1}

NMR ($CDCl_3$, δ): 1.7–2.0 (6H, m), 3.45 (2H, t, J=6.7Hz), 3.93 (3H, s), 4.02 (2H, t, J=6.1Hz), 6.97 (2H, d, J=8.7Hz), 7.56 (2H, d, J=8.7Hz), 7.61 (2H, d, J=8.3Hz), 8.07 (2H, d, J=8.3Hz)

APCI-MASS: m/z=378 $(M+H)^+$

Preparation 77

Methyl 4-[4-(5-phenoxypentyloxy)phenyl]benzoate

IR (KBr): 2944, 2931, 1720, 1600, 1492, 1197, 1110 cm^{-1}

NMR ($CDCl_3$, δ): 1.6–1.8 (2H, m), 1.8–2.0 (4H, m), 3.93 (3H, s), 4.00 (2H, t, J=6.3Hz), 4.04 (2H, t, J=6.3Hz), 6.9–7.1 (5H, m), 7.3–7.4 (2H, m), 7.56 (2H, d, J=8.7Hz), 7.62 (2H, d, J=8.3Hz), 8.07 (2H, d, J=8.3Hz)

APCI-MASS: m/z=391 $(M+H)^+$

Preparation 78

1-[2-(4-Cyclohexylphenylamino)ethyl]-2-oxazolidone hydrochloride

IR (KBr): 2923.6, 2852.2, 1747.2, 1683.6 cm^{-1}

NMR (DMSO-d_6, δ): 1.1–1.5 (6H, m), 1.6–1.9 (4H, m, 2.3–2.6 (1H, m), 3.3–3.5 (4H, m), 3.58 (2H, dd, J=9.4 and 7.4Hz), 4.22 (2H, dd, J=9.4 and 7.4 Hz), 7.1–7.4 (4H, m)

Preparation 79

Methyl 4-[4-(8-hydroxyoctyloxy)phenyl]benzoate

IR (KBr): 3250, 2933, 2856, 1724, 1602, 1436, 1292, 1199 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.9 (12H, m), 3.6–3.8 (2H, br), 3.93 (3H, s), 4.00 (2H, t, J=6.7Hz), 4.82 (1H, s), 7.68 (2H, d, J=8.7Hz), 7.56 (2H, d, J=8.7Hz), 7.62 (2H, d, J=8.3Hz), 8.07 (2H, d, J=8.3Hz)

APCI-MASS: m/z=357 $(M+H^+)$

Preparation 80

Methyl 4-[4-(6-bromohexyloxy)phenyl]benzoate

IR (KBr): 2937, 2861, 1724, 1602, 1529, 1436, 1292, 1199, 1112 cm^{-1}

NMR ($CDCl_3$, δ): 1.5–2.0 (8H, m), 3.43 (2H, t, J=6.8Hz), 3.93 (3H, s), 4.02 (2H, t, J=6.3Hz), 6.98 (2H, d, J=8.8Hz), 7.56 (2H, d, J=8.8Hz), 7.62 (2H, d, J=8.4Hz), 8.07 (2H, d, J=8.4Hz)

APCI-MASS: m/z=391 $(M+H^+)$

Preparation 81

Methyl 4-[4-(5-Bromopentyloxy)phenyl] bromobenzene

IR (KBr): 2942, 2867, 1604, 1515, 1477, 1286 cm^{-1}

NMR ($CDCl_3$, δ): 1.5–2.0 (6H, m), 3.44 (2H, t, J=6.7Hz), 3.99 (2H, t, J=6.2Hz), 6.95 (2H, d, J=8.7Hz), 7.3–7.6 (6H, m)

APCI-MASS: m/z=399 $(M+H^+)$

Preparation 82

8-[4-(4-Methoxycarbonyloxy)phenoxy]octanoyl piperidine

IR (KBr): 2935, 2852, 1720, 1639, 1604, 1438, 1292 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.9 (16H, m), 2.34 (2H, d, J=7.6Hz), 3.4–3.6 (4H, m), 3.93 (3H, s), 3.99 (2H, t, J=6.4Hz), 6.97 (2H, d, J=8.8Hz), 7.55 (2H, d, J=8.8Hz), 7.61 (2H, d, J=8.6Hz), 8.07 (2H, d J=8.6Hz)

APCI-MASS: m/z=438 $(M+H^+)$

Preparation 83

Methyl 6-[4-(4-n-heptyloxyphenyl)piperazin-1-yl] nicotinate

IR (KBr): 2933, 2859, 1726, 1608, 1513, 1430, 1280, 1245 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7Hz), 1.2–1.8 (10H, m), 3.17 (4H, t, J=4.9Hz), 3.8–4.0 (9H, m), 6.65 (1H, d, J=9.1Hz), 6.86 (2H, d, J=9.1Hz), 6.96 (2H, d, J=9.1Hz), 8.05 (1H, dd, J=9.1 and 2.3 Hz), 8.82 (1H, d, J=2.3Hz)

APCI-MASS: m/z=412 $(M+H^+)$

Preparation 84

Methyl 6-[4-[4-(8-bromooctyloxy)phenyl]piperazin-1-yl]nicotinate

IR (KBr): 2933, 2861, 1724, 1608, 1513, 1430, 1280 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–2.0 (12H, m), 3.17 (4H, t, J=5.0Hz), 3.40 (2H, t, J=6.8Hz), 3.8–4.0 (9H, m), 6.64 (1H, d, J=9.0Hz), 6.85 (2H, d, J=9.1Hz), 6.96 (2H, d, J=9.1Hz), 8.05 (1H, dd, J=9.0 and 2.2Hz), 8.82 (1H, d, J=2.2Hz)

APCI-MASS: m/z=504 $(M+H^+)$

Preparation 85

4-[4-(7-Bromoheptyloxy)phenyl]bromobenzene

IR (KBr): 2935.1, 2856.1, 1604.5 cm^{-1}

NMR ($CDCl_3$, δ): 1.18–1.65 (6H, m), 1.70–2.02 (4H, m), 3.41 (2H, t, J=6.8Hz), 3.99 (2H, t, J=6.4Hz), 6.95 (2H, d, J=8.6Hz), 7.40 (2H, d, J=8.6Hz), 7.46 (2H, d, J=8.6Hz), 7.52 (2H, d, J=8.6Hz)

Preparation 86

4-[4-(8-Bromooctyloxy)phenyl]bromobenzene

NMR ($CDCl_3$, δ): 1.22–1.65 (8H, m), 1.65–1.95 (4H, m), 3.41 (2H, t, J=6.8Hz), 3.99 (2H, t, J=6.4Hz), 6.95 (2H, d,

J=8.6Hz), 7.40 (2H, d, J=8.6Hz), 7.46 (2H, d, J=8.6Hz), 7.52 (2H, d, J=8.6Hz)

Preparation 87

Methyl (E)-3-[4-[4-(5-hexenyloxy)phenyl]phenyl] acrylate

NMR ($CDCl_3$, δ): 1.50–1.72 (2H, m), 1.72–1.95 (2H, m), 2.05–2.14 (2H, m), 3.82 (3H, s), 4.01 (2H, t, J=6.3Hz), 4.95–5.10 (2H, m), 5.70–5.93 (1H, m), 6.46 (1H, d, J=16Hz), 6.97 (2H, d, J=8.7Hz), 7.54 (2H, d, J=8.7Hz), 7.58 (4H, s), 7.72 (1H, d, J=16Hz)

APCI-MASS: m/z=337 (M^++1)

Preparation 88

4-Bromo-4'-(4-methylpentyloxy)biphenyl

IR (KBr): 2956.3, 2871.5, 1606.4 cm^{-1}

NMR ($CDCl_3$, δ): 0.93 (6H, d, J=6.6Hz), 1.25–1.45 (2H, m), 1.62 (1H, sept, J=6.6Hz), 1.72–1.93 (2H, m), 3.98 (2H, d, J=6.6Hz), 6.95 (2H, d, J=8.6Hz), 7.30–7.60 (6H, m)

APCI-MASS: m/z=332, 334 (M^+, M^++2)

The following compounds (Preparations 89 to 90) were obtained according to a similar manner to that of Preparation 2.

Preparation 89

N-[4-[2-(4-Methylpentyl)-2,3-dihydro-4H-1,2,4-triazol-3-one-4-yl]phenyl]piperazine ditrifluoroacetate

IR (KBr): 1668.1, 1519.6, 1203.4, 1176.4, 1130.1 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (6H, d, J=6.6Hz), 1.1–1.3 (2H, m), 1.4–1.8 (3H, m), 3.1–3.3 (4H, m), 3.3–3.5 (4H, m), 3.70 (2H, t, J=7.0Hz), 7.11 (2H, d, J=9.0Hz), 7.53 (2H, d, J=9.0Hz), 8.35 (1H, s), 8.90 (2H, s)

Preparation 90

1-(4-Phenylcyclohexyl)piperazine ditrifluoroacetate

IR (KBr): 1677.8, 1197.6, 1133.9 cm^{-1}

NMR (DMSO-d_6, δ): 1.4–1.8 (4H, m), 1.8–2.25 (4H, m), 2.4–2.7 (1H, m), 3.2–3.7 (9H, m), 4.54 (2H, br s), 7.0–7.4 (5H, m), 9.32 (1H, br s)

APCI-MASS: m/z=245 (M^++H)

The following compounds (Preparations 91 to 103) were obtained according to a similar manner to that of Preparation 3.

Preparation 91

Methyl 6-[4-(4-octyloxyphenyl)piperazin-1-yl] nicotinate

IR (KBr): 2923, 1726, 1608, 1515, 1278, 1116 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.8Hz), 1.2–1.5 (10H, m), 1.7–1.8 (2H, m), 3.1–3.2 (4H, m), 3.8–4.0 (9H, m), 6.64 (1H, d, J=9.0Hz), 6.8–7.0 (4H, m), 8.04 (1H, dd, J=9.0 and 2.4Hz), 8.81 (1H, d, J=2.4Hz)

APCI-MASS: m/z=426 (M+H^+)

Preparation 92

4-[4-[4-[2-(4-Methylpentyl)-2,3-dihydro-4H-1,2,4-triazol-3-one-4-yl]phenyl]piperazin-1-yl]benzonitrile

IR (KBr): 2217.7, 1685.5 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (6H, d, J=6.6Hz), 1.2–1.4 (2H, m), 1.5–2.0 (3H, m), 3.3–3.4 (4H, m), 3.4–3.6 (4H, m), 3.83 (2H, t, J=7.4Hz), 6.92 (2H, d, J=9.0Hz), 7.01 (2H, d, J=9.0Hz) 7.43 (2H, d, J=9.0Hz), 7.54 (2H, d, J=9.0Hz), 7.62 (1H, s)

Preparation 93

3-Fluoro-4-[4-(4-methoxyphenyl)piperazin-1-yl] benzonitrile

IR (KBr): 2225.5, 1510.0, 1240.0 cm^{-1}

NMR ($CDCl_3$, δ): 3.1–3.55 (8H, m), 3.79 (3H, s), 6.7–7.1 (6H, m), 7.3–7.5 (1H, m)

Preparation 94

3-Chloro-4-[4-(4-n-hexyloxyphenyl)piperazin-1-yl] benzonitrile

IR (KBr): 2223.5, 1592.9, 1510.0, 1490.7, 1236.1 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.7Hz), 1.3–1.6 (6H, m), 1.7–1.9 (2H, m), 3.2–3.4 (8H, m), 3.92 (2H, t, J=6.6Hz), 6.85 (2H, d, J=9.3Hz), 6.94 (2H, d, J=9.3Hz), 7.08 (1H, d, J=8.4Hz), 7.53 (1H, dd, J=8.4 and 1.9Hz), 7.64 (1H, d, J=1.9Hz)

APCI-MASS: m/z=398 (M^++H)

Preparation 95

Ethyl 3-[4-(4-n-hexyloxyphenyl)piperazin-1-yl]-6-pyridazinecarboxylate

IR (KBr): 1729.8, 1587.1, 1511.9, 1245.8 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5Hz), 1.2–1.4 (6H, m), 1.44 (3H, t, J=7.1Hz), 1.65–1.85 (2H, m), 3.1–3.25 (4H, m), 3.8–4.0 (6H, m), 4.46 (2H, q, J=7.1Hz), 6.8–7.0 (5H, m), 7.91 (1H, d, J=9.6Hz)

APCI-MASS: m/z=413 (M^++H)

Preparation 96

4-(4-Piperidinopiperidin-1-yl)benzonitrile

IR (KBr): 2217.7, 1602.6, 1511.9 cm^{-1}

NMR ($CDCl_3$, δ): 1.35–1.75 (8H, m), 1.92 (2H, d, J=12.9Hz), 2.3–2.6 (5H, m), 2.86 (2H, td, J=12.8 and 2.6Hz), 3.90 (2H, d, J=12.8Hz), 6.84 (2H, d, J=9.1Hz), 7.46 (2H, d, J=9.1Hz)

APCI-MASS: m/z=270 (M^++H)

Preparation 97

5-[4-(4-n-Hexyloxyphenyl)piperazin-1-yl] picolinonitrile

IR (KBr): 2223.5, 1575.6, 1511.9, 1241.9 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5Hz), 1.2–1.55 (6H, m), 1.7–1.85 (2H, m), 3.22 (4H, t, J=5.1Hz), 3.52 (4H, t, J=5.1Hz), 3.92 (2H, t, J=6.5Hz), 6.86 (2H, d, J=9.4Hz), 6.93 (2H, d, J=9.4Hz), 7.13 (1H, dd, J=8.8 and 3.0Hz), 7.53 (1H, d, J=8.8Hz), 8.35 (1H, d, J=3.0Hz)

APCI-MASS: m/z=365 (M^++H)

Preparation 98

4-[4-(4- Cyclohexylphenyl)piperazin-1-yl] benzonitrile

IR (KBr): 2219.7, 1606.4, 1513.8, 1238.1 cm^{-1}

NMR ($CDCl_3$, δ): 1.1–1.5 (6H, m), 1.65–2.0 (4H, m), 2.44 (1H, m), 3.30 (4H, t, J=5.1Hz), 3.46 (4H, t, J=5.1Hz), 6.90 (4H, d, J=8.9Hz), 7.14 (2H, d, J=8.9Hz), 7.52 (2H, d, J=8.9Hz)

APCI-MASS: m/z=346 (M^++H)

Preparation 99

4-[4-(4-n-Hexylphenyl)piperazin-1-yl]benzonitrile

IR (KBr): 2925.5, 2850.3, 2213.9, 1604.5, 1513.8, 1234.2, 944.9 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.4Hz), 1.2–1.45 (6H, m), 1.45–1.7 (2H, m), 2.54 (2H, t, J=7.6Hz), 3.2–3.4 (4H, m), 3.4–3.6 (4H, m), 6.89 (2H, d, J=8.5Hz), 6.91 (2H, d, J=8.9Hz), 7.11 (2H, d, J=8.5Hz), 7.52 (2H, d, J=8.9Hz)

Preparation 100

1-[2-(4-n-Hexylphenylamino)ethyl]-2-oxazolidone hydrochloride

IR (KBr): 2925.5, 2852.2, 1753.0, 1729.8, 1267.0 cm^{-1}

NMR ($CDCl_3$, δ): 0.85 (3H, t, J=6.5Hz), 1.1–1.4 (6H, m), 1.45–1.7 (2H, m), 2.56 (2H, t, J=7.6Hz), 3.3–3.53 (4H, m), 3.57 (2H, t, J=7.9Hz), 4.24 (2H, t, J=7.9Hz), 7.24 (4H, s)

APCI-MASS: m/z=291 (M^++H)

Preparation 101

4-[4-(4-Phenylcyclohexyl)piperazin-1-yl] benzonitrile

IR (KBr): 2212.0, 1602.6, 1513.8, 1249.6 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.8 (4H, m), 1.9–2.2 (4H, m), 2.3–2.6 (2H, m), 2.75 (4H, t, J=5.0Hz), 3.34 (4H, t, J=5.0Hz), 6.86 (2H, d, J=8.9Hz), 7.1–7.4 (5H, m), 7.49 (2H, d, J=8.9Hz)

APCI-MASS: m/z=346 (M^++H)

Preparation 102

Methyl 6-[4-(4-hydroxyphenyl)piperazin-1-yl] nictinate

IR (KBr): 3411, 1691, 1602, 1510, 1432, 1249, 1147 cm^{-1}

NMR ($DMSO_6$, δ): 3.0–3.1 (4H, m), 3.7–3.9 (7H, m), 6.67 (2H, d, J=8.8Hz), 6.84 (2H, d, J=8.8Hz), 6.93 (1H, d, J=9.1Hz), 7.97 (1H, dd, J=2.4 and 9.1Hz), 8.66 (1H, d, J=2.4Hz), 8.88 (1H, s)

APCI-MASS: m/z=314 $(M+H)^+$

Preparation 103

1-n-Decylindole-5-carboxylic acid

IR (KBr): 2921, 2854, 1679, 1612, 1427, 1313, 1199 cm^{-1}

NMR ($DMSO_6$, δ): 0.84 (3H, t, J=6.8Hz), 1.1–1.3 (14H, m), 1.6–1.8 (2H, m), 4.19 (2H, t, J=6.9Hz), 6.57 (1H, s), 7.4–7.8 (3H, m), 8.23 (1H, s), 12.40 (1H, s)

APCI-MASS: m/z=302 ($M+H^+$)

The following compounds (Preparations 104 to 111) were obtained according to a similar manner to that of Preparation 10.

Preparation 104

(E)-Methyl 4-(4-n-butoxyphenyl)cinnamate

IR (KBr): 2958, 2939, 2873, 1720, 1637, 1498, 1313, 1195, 1170 cm^{-1}

NMR ($CDCl_3$, δ): 0.98 (3H, t, J=7.3Hz), 1.4–1.8 (4H, m), 3.81 (3H, s), 4.00 (2H, t, J=6.4Hz), 6.45 (1H, d, J=16.0Hz), 6.97 (2H, d, J=8.7Hz), 7.5–7.7 (6H, m), 7.72 (1H, d, J=16.0Hz)

APCI-MASS: m/z=311 ($M+H^+$)

Preparation 105

Methyl (E)-3-[4-[4-(4-methylpentyloxy)phenyl] phenyl]acrylate

IR (KBr): 2956.3, 2873.4, 1720.2, 1635.3, 1600.6 cm^{-1}

NMR ($CDCl_3$, δ): 0.93 (6H, d, J=6.5Hz), 1.28–1.50 (2H, m), 1.50–1.95 (3H, m), 3.82 (3H, s), 3.99 (2H, t, J=6.6Hz), 6.44 (1H, d, J=16.0Hz), 6.97 (2H, d, J=8.7Hz), 7.49–7.65 (6H, m), 7.71 (1H, d, J=16Hz)

APCI-MASS: m/z=339 (M^++1)

Preparation 106

Methyl (E)-3-[4-[4-(6-fluorohexyloxy)phenyl] phenyl]acrylate

NMR ($CDCl_3$, δ): 1.23–2.00 (8H, m), 3.81 (3H, s), 4.01 (2H, t, J=6.4Hz), 4.47 (2H, dt, J=47.4 and 6.0Hz), 6.45 (1H, d, J=16.0Hz), 6.96 (2H, d, J=8.8Hz), 7.45–7.63 (6H, m), 7.72 (1H, d, J=16.0Hz)

APCI-MASS: m/z=357 (M^++1)

Preparation 107

Methyl (E)-3-[4-[4-(6-methoxyhexyloxy)phenyl] phenyl]acrylate

APCI-MASS: m/z=369 (M^+)

Preparation 108

Methyl (E)-3-[4-[4-(8-methoxyoctyloxy)phenyl] phenyl]acrylate

IR (KBr): 2935.1, 2858.0, 1722.1, 1637.3, 1602.6 cm^{-1}

NMR ($CDCl_3$, δ): 1.30–1.70 (10H, m), 1.70–1.92 (2H, m), 3.33 (3H, s), 3.37 (2H, t, J=6.5Hz), 3.81 (3H, s), 4.00 (2H, t, J=6.5Hz), 6.45 (1H, d, J=16.0Hz), 6.97 (2H, d, J=8.8Hz), 7.46–7.78 (6H, m), 7.72 (1H, d, J=16.0Hz)

APCI-MASS: m/z=397 (M^++1)

Preparation 109

Methyl (E)-3-[4-(8-hydroxyphenyl)phenyl]acrylate

IR (KBr): 3409.5, 1695.1 cm^{-1}

NMR ($DMSO_6$, δ): 3.73 (3H, s), 6.64 (1H, d, J=16Hz), 6.85 (2H, d, J=8.6Hz), 7.50–7.83 (5H, m)

APCI-MASS: m/z=255 (M^++1)

Preparation 110

Methyl (E)-3-[4-[4-(7-methoxyheptyloxy)phenyl] phenyl]acrylate

NMR ($CDCl_3$, δ): 1.32–1.70 (8H, m), 1.70–1.92 (2H, m), 3.34 (3H, s), 3.38 (2H, t, J=6.4Hz), 3.81 (3H, s), 4.00 (2H,

t, J=6.5Hz), 6.45 (1H, d, J=16.0Hz), 6.97 (2H, d, J=8.8Hz), 7.74–7.65 (6H, m), 7.70 (1H, d, J=16Hz)

APCI-MASS: m/z=383 (M^++1)

Preparation 111

Methyl (E)-3-[4-[4-(7-fluoroheptyloxy)phenyl] phenyl]acrylate

(KBr): 2937.1, 2861.8, 1722.1, 1637.3, 1600.6 cm^{-1}

The following compound was obtained according to a similar manner to that of Preparation 20.

Preparation 112

Methyl 3-[4-(4-heptylphenyl)phenyl]propanoate

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.5Hz), 1.15–1.50 (8H, m); 1.50–1.77 (2H, m), 2.52–2.73 (4H, m), 2.99 (2H, t, J=7.8Hz), 3.68 (3H, s), 7.18–7.35 (4H, m), 7.40–7.58 (4H, m)

APCI-MASS: m/z=339 (M^++1)

The following compounds (Preparation 113 to 164) were obtained according to a similar manner to that of Preparation 32.

Preparation 113

4-(4-Octylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one-2-yl-acetic acid

IR (KBr): 2923.6, 1704.8, 1224.6 cm^{-1}

NMR ($DMSO_6$, δ): 0.85 (3H, t, J=6.7Hz), 1.1–1.4 (10H, m), 1.4–1.7 (2, H, m), 2.60 (2H, t, J=7.2Hz), 4.38 (2H, s), 7.32 (2H, d, J=8.5Hz), 7.58 (2H, d, J=8.5Hz), 8.43 (1H, s)

Preparation 114

1-Heptyl-4-(4-carboxyphenyl)pyrazole

IR (KBr): 3106, 2917, 1687, 1612, 1425, 1295, 1184, 952, 860, 773 cm^{-1}

NMR ($DMSO_6$, δ): 0.85 (3H, t, J=6.8Hz), 1.1–1.4 (8H, m), 1.7–1.9 (2H, m), 4.11 (2H, t, J=7.0Hz), 7.69 (2H, d, J=8.5Hz), 7.91 (2H, d, J=8.5Hz), 7.98 (1H, s), 8.32 (1H, s), 12.82 (1H, br)

APCI-MASS: m/z=287 ($M+H^+$)

Preparation 115

6-[4-(4-Octyloxyphenyl)piperazin-1-yl]nicotinic acid

IR (KBr pelet): 2919, 2854, 1697, 1608, 1515, 1429, 1263, 1245, 1228 cm^{-1}

NMR ($DMSO_6$, δ): 0.86 (3H, t, J=6.7Hz), 1.1–1.5 (10H, m), 1.6–1.8 (2H, m), 3.0–3.2 (4H, m), 3.7–3.9 (4H, m), 3.88 (2H, t, J=6.4Hz), 6.7–7.0 (5H, m), 7.95 (1H, dd, J=9.0 and 1.1Hz), 8.64 (1H, d, J=1.1Hz)

APCI-MASS: m/z=412 ($M+H^+$)

Preparation 116

2-(4-Hexyloxyphenyl)benzoxazole-5-carboxylic acid

IR (KBr): 2952, 1689, 1677, 1619, 1500, 1415, 1299, 1172, 1024 cm^{-1}

NMR ($DMSO_6$, δ): 0.89 (3H, t, J=6.7Hz), 1.2–1.5 (6H, m), 1.7–1.9 (2H, m), 4.09 (2H, t, J=6.5Hz), 7.16 (2H, d, J=8.8Hz), 7.84 (1H, d, J=8.5Hz), 8.01 (1H, dd, J=8.5 and 1.5Hz), 8.15 (2H, d, J=8.8Hz), 8.26 (1H, d, J=1.5Hz)

APCI-MASS: m/z=340 ($M+H^+$)

Preparation 117

4-[4-(4-n-Butyloxyphenyl)phenyl]benzoic acid

IR (KBr): 2958, 2873, 1689, 1600, 1537, 1396 cm^{-1}

Preparation 118

6-(4-Heptyloxyphenyl)nicotinic acid

IR (KBr): 2858, 1699, 1674, 1589, 1425, 1180, 1016, 781 cm^{-1}

NMR ($DMSO_6$, δ): 0.87 (3H, t, J=6.7Hz), 1.2–1.5 (8H, m), 1.6–1.8 (2H, m), 4.04 (2H, t, J=6.4Hz), 7.06 (2H, d, J=8.9Hz), 8.03 (1H, d, J=8.2Hz), 8.13 (2H, d, J=8.9Hz), 8.27 (1H, dd, J=8.2 and 2.2Hz), 9.09 (1H, d, J=2.2Hz), 13.31 (1H, br)

APCI-MASS: m/z=314 ($M+H^+$)

Preparation 119

5-(4-Octyloxyphenyl)isoxazole-3-carboxylic acid

IR (KBr pelet): 2923, 2852, 1704, 1612, 1440, 1272, 1178 cm^{-1}

NMR ($DMSO_6$, δ): 0.86 (3H, t, J=6.8Hz), 1.2–1.6 (10H, m), 1.6–1.9 (2H, m), 4.03 (2H, t, J=6.5Hz), 7.08 (2H, d, J=8.9Hz), 7.25 (1H, s), 7.86 (2H, d, J=8.9Hz)

APCI-MASS: m/z=318 ($M+H^+$)

Preparation 120

2-(2-Octyloxypyridin-5-yl)benzoxazole-5-carboxylic acid

IR (KBr): 2954, 2923, 2854, 1697, 1683, 1625, 1488, 1290 cm^{-1}

NMR ($DMSO_6$, δ): 0.86 (3H, t, J=7.6Hz), 1.2–1.5 (10H, m), 1.7–1.8 (2H, m), 4.36 (2H, t, J=6.6Hz), 7.04 (1H, d, J=8.7Hz), 7.88 (1H, d, J=8.5Hz), 8.04 (1H, dd, J=8.5 and 1.6Hz), 8.29 (1H, d, J=1.6Hz), 8.43 (1H, dd, J=8.7 and 2.4Hz), 8.99 (1H, d, J=2.4Hz), 13.0–13.2 (1H, br)

APCI-MASS: m/z=369 ($M+H^+$)

Preparation 121

2-[4-(4-Hexylphenyl)phenyl]benzoxazole-5-carboxylic acid

IR (KBr): 2923, 2854, 1683, 1411, 1299, 1054 cm^{-1}

APCI-MASS: m/z=400 ($M+H^+$)

Preparation 122

6-[4-(4-n-Butyloxyphenyl)phenyl]nicotinic acid

IR (KBr): 3406, 2958, 1691, 1591, 1394, 1284, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 0.94 (3H, t, J=7.3Hz), 1.4–1.8 (4H, m), 4.01 (2H, t, J=6.4Hz), 7.02 (2H, d, J=8.7Hz), 7.57 (2H, d, J=8.7Hz), 7.61 (2H, d, J=8.2Hz), 7.83 (2H, d, J=8.2Hz), 8.05 (1H, d, J=8.5Hz), 8.22 (1H, dd, J=8.5 and 1.6Hz), 9.14 (1H, d, J=1.6Hz)

APCI-MASS: m/z=348 ($M+H^+$)

Preparation 123

4-[4-(5-Phenoxypentyloxy)phenyl]benzoic acid

NMR (DMSO-d_6, δ): 1.5–1.7 (2H, m), 1.7–1.9 (4H, m), 3.98 (2H, t, J=6.3Hz), 4.05 (2H, t, J=6.1Hz), 6.8–7.0 (3H,

m), 7.05 (2H, d, J=8.6Hz), 7.25 (2H, t, J=8.2Hz), 7.68 (2H, d, J=8.5Hz), 7.75 (2H, d, J=8.2Hz), 7.98 (2H, d, J=8.2Hz), 12.8–13.0 (1H, br s)

APCI-MASS: m/z=375 $(M-H)^-$

Preparation 124

4-[5-(4-Hexyloxyphenyl)-1,3,4-oxadiazol-2-yl] benzoic acid

IR (KBr): 2935, 2854, 1685, 1612, 1495, 1425, 1286, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7Hz), 1.2–1.5 (6H, m), 1.6–1.9 (3H, m), 4.12 (2H, t, J=6.4Hz), 7.19 (2H, d, J=8.7Hz), 8.08 (2H, d, J=8.7Hz), 8.18 (2H, d, J=8.4Hz), 8.24 (2H, d, J=8.4Hz)

APCI-MASS: m/z=367 $(M+H)^+$

Preparation 125

4-[5-(4-Hexyloxyphenyl)-1,3,4-thiadiazol-2-yl] benzoic acid

IR (KBr): 2952, 2586, 1699, 1604, 1517, 1432, 1251, 1174 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7Hz), 1.3–1.9 (8H, m), 4.04 (2H, t, J=6.3Hz), 7.13 (2H, d, J=8.8Hz), 7.97 (2H, d, J=8.8Hz), 8.11 (4H, s)

APCI-MASS: m/z=383 $(M+H)^+$

Preparation 126

5-(4-Octyloxyphenyl)-1-methylpyrazole-3-carboxyic acid

IR (KBr pelet): 2950, 2923, 1695, 1450, 1282, 1251, 956 cm^{-1}

NMR ($DMSO_6$, δ): 0.86 (3H, t, J=6.8Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 3.98 (2H, t, J=6.5Hz), 4.10 (3H, s), 6.95 (1H, d, J=8.8Hz), 7.18 (1H, s), 7.73 (2H, d, J=8.8Hz), 13.37 (1H, br)

APCI-MASS: m/z=331 $(M+H^+)$

Preparation 127

4-[3-(4-n-Pentyloxyphenyl)pyrazol-5-yl]benzoic acid

IR (KBr): 3224, 2956, 1692, 1614, 1506, 1251 cm^{-1}

NMR ($DMSO_6$, δ): 0.91 (3H, t, J=6.9Hz), 1.3–1.5 (4H, m), 1.6–1.8 (2H, m), 4.00 (2H, t, J=6.5Hz), 7.02 (2H, d, J=8.8Hz), 7.19 (1H, s), 7.75 (2H, d, J=8.8Hz), 7.95 (2H, d, J=8.7Hz), 8.02 (2H, d, J=8.7Hz), 12.8–13.3 (2H, br)

APCI-MASS: m/z=351 $(M+H^+)$

Preparation 128

5-[4-(4n-Butoxyphenyl)phenyl]furan-2-carboxylic acid

IR (KBr): 2958, 2873, 1679, 1487, 1253, 1166 cm^{-1}

NMR ($DMSO_6$, δ): 0.95 (3H, t, J=7.3Hz), 1.3–1.8 (4H, m), 4.02 (2H, t, J=6.3Hz), 7.03 (2H, d, J=8.6Hz), 7.17 (1H, d, J=3.6Hz), 7.33 (1H, d, J=3.6Hz), 7.66 (2H, d, J=8.6Hz), 7.74 (2H, d, J=8.4Hz), 7.86 (2H, d, J=8.4Hz), 13.1 (1H, br s)

APCI-MASS: m/z=337 $(M+H)^+$

Preparation 129

3-(S)-Hydroxyhexadecanoic acid

IR (KBr): 1679.7, 1467.6, 1224.6 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.4Hz), 1.1–1.7 (24H, m), 2.35–2.65 (2H, m), 4.03 (1H, m), 5.41 (1H, br s)

Preparation 130

6-[4-(4-n-Hexyloxyphenyl)piperazin-1-yl] pyridazine-3-carboxylic acid

IR (KBr): 1697.1, 1589.1, 1515.8, 1448.3 cm^{-1}

NMR ($DMSO_6$, δ): 0.87 (3H, t, J=6.4Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 3.0–3.2 (4H, m), 3.7–4.0 (6H, m), 6.83 (2H, d, J=9.0Hz), 6.95 (2H, d, J=9.0Hz), 7.36 (1H, d, J=9.6Hz), 7.86 (1H, d, J=9.6Hz), 11.68 (1H, s)

Preparation 131

4-[4-[1-(4-n-Hexyloxyphenyl)piperidin-4-yl] piperazin-1-yl]benzoic acid hydrochloride

IR (KBr): 1699.0, 1608.3, 1513.8 cm^{-1}

NMR ($DMSO_6$, δ): 0.88 (3H, t, J=6.5Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 2.0–2.45 (3H, m), 3.2–3.8 (12H, m), 3.94 (2H, t, J=6.4Hz), 4.03 (2H, d, J=11Hz), 6.95 (2H, d, J=8.7Hz), 7.07 (2H, d, J=8.9Hz), 7.32 (2H, br s), 7.83 (2H, d, J=8.9Hz)

APCI-MASS: m/z=466 (M^+H)

Preparation 132

6-(8-Methoxyoctyloxy)-2-naphtholic acid

IR (KBr): 2937.1, 2854.1, 1677.8, 1211.1 cm^{-1}

NMR ($DMSO_6$, δ): 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.5Hz), 4.11 (2H, t, J=6.4Hz), 7.23 (1H, dd, J=9.0 and 2.3Hz), 7.39 (1H, d, J=2.3Hz), 7.85 (1H, d, J=8.7Hz), 7.93 (1H, d, J=8.7Hz), 7.99 (1H, d, J=9.0Hz), 8.51 (1H, s), 12.9 (1H, s)

Preparation 133

Mixture of (E) and (Z)-3-[4-(4-Heptylphenyl)phenyl]-2-butenoic acid

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6Hz), 1.15–1.50 (8H, m), 1.52–1.75 (2H, m), 2.63 and 3.62 (total 3H, each s), 2.53–2.75 (2H, m), 6.24 and 5.68 (total 1H, each s), 7.19–7.35 (2H, m), 7.47–7.70 (6H, m)

APCI-MASS: m/z=337 $(M^+{+}1)$, 351 (methyl ester$^+$+1)

Preparation 134

3-[4-(4-Heptylphenyl)phenyl]propanoic acid

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6Hz), 1.13–1.48 (8H, m), 1.48–1.75 (2H, m), 2.52–2.83 (4H, m), 3.00 (2H, t, J=7.8Hz), 7.15–7.35 (4H, m), 7.40–7.60 (4H, m)

APCI-MASS: m/z=323 $(M^+{-}1)$

Preparation 135

4-(4-Heptylphenyl)benzoyl-carboxylic acid

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6Hz), 1.13–1.50 (8H, m), 1.50–1.75 (2H, m), 2.66 (2H, t, J=7.7Hz), 7.20–7.40 (2H, m), 7.50–7.66 (2H, m), 7.66–7.84 (2H, m), 8.40–8.60 (2H, m)

APCI-MASS: m/z=323 $(M^+{-}1)$

Preparation 135

6-Hexylnaphthalene-2carboxylic acid

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8Hz), 1.15–1.53 (6H, m), 1.55–1.84 (2H, m), 2.80 (2H, t, J=7.6Hz), 7.42 (1H, dd,

J=1.7 and 8.4Hz), 7.67 (1H, s) 7.84 (1H, d, J=8.6Hz), 7.90 (1H, d, J=8.4Hz), 8.09 (1H, dd, J=1.7 and 8.6Hz), 8.68 (1H, s) p APCI-MASS: m/z=257 (M^++1), 271 (methyl ester$^+$+1)

Preparation 137

3-(E)-[4-[4-(7-Methoxyheptyloxy)phenyl]phenyl] acrylic acid

NMR ($DMSO_6$, δ): 1.20–1.60 (8H, m), 1.60–1.83 (2H, m), 3.21 (3H, s), 3.25–3.60 (2H, m), 4.01 (2H, t, J=6.4Hz), 6.54 (1H, d, J=16.0Hz), 7.02 (2H, d, J=8.8Hz), 7.55–7.80 (7H, m)

APCI-MASS: m/z=369 (M^++1)

Preparation 138

3-(E)-[4-[4-(8-Methoxyoctyloxy)phenyl]phenyl] acrylic acid

IR (KBr): 3037.3, 2933.2, 2858.0, 2551.4, 1706.7, 1677.8, 1629.6, 1602.6 cm^{-1}

NMR ($DMSO_6$, δ): 1.18–1.55 (10H, m), 1.65–1.83 (2H, m), 3.18–3.45 (5H, m), 4.01 (2H, t, J=6.5Hz), 6.53 (1H, d, J=16.0Hz), 7.02 (2H, d, J=8.8Hz), 7.50–8.80 (7H, m)

APCI-MASS: m/z=383 (M^++1)

Preparation 139

3-(E)-[4-[4-(5-Hexenyloxy)phenyl]phenyl]acrylic acid

NMR ($DMSO_6$, δ): 1.42–1.63 (2H, m), 1.63–1.85 (2H, m), 2.00–2.20 (2H, m), 4.03 (2H, t, J=6.3Hz), 4.90–5.15 (2H, m), 5.68–5.97 (1H, m), 6.54 (1H, d, J=16Hz), 7.02 (2H, d, J=8.7Hz), 7.50–7.80 (7H, m)

APCI-MASS: m/z=323 (M^++1)

Preparation 140

3-(E)-[4-[4-(4-Methylpentyloxy)phenyl]phenyl] acrylic acid

IR (KBr): 2956.3, 2869.6, 2713.4, 2599.6, 1689.3, 1627.6, 1602.6 cm^{-1}

NMR ($DMSO_6$, δ): 0.89 (6H, d, J=6.5Hz), 1.15–1.43 (2H, m), 1.48–1.90 (3H, m), 4.00 (2H, t, J=6.7Hz), 6.54 (1H, d, J=16Hz), 7.02 (2H, d, J=8.7Hz), 7.50–7.90 (7H, m)

APCI-MASS: m/z=325 (M^++1)

Preparation 141

3-(E)-[4-[4-(6-Fluorohexyloxy)phenyl]phenyl] acrylic acid

NMR ($CDCl_3$, δ): 1.39–2.00 (8H, m), 4.01 (2H, t, J=6.5Hz) 4.47 (2H, dt, J=47.3 and 6.0Hz), 6.49 (1H, d, J=15.9Hz), 6.98 (2H, d, J=8.7Hz), 7.40–7.70 (6H, m), 7.81 (1H, d, J=15.9Hz)

APCI-MASS: m/z=343 (M^++1)

Preparation 142

3-(E)-[4-[4-(6-Methoxyhexyloxy)phenyl]phenyl] acrylic acid

NMR ($DMSO_6$, δ): 1.22–1.63 (6H, m), 1.63–1.88 (2H, m), 3.21 (3H, s), 3.22–3.40 (2H, m), 4.00 (2H, t, J=6.5Hz), 6.54 (1H, d, J=15.8Hz), 7.02 (2H, d, J=8.7Hz), 7.50–7.84 (7H, m)

APCI-MASS: m/z=369 (methyl ester, M^++1)

Preparation 143

4-[4-[8-(Tetrahydropyran-2-yl-oxy)octyloxy]phenyl] benzoic acid

IR (KBr): 2935, 1697, 1683, 1604, 1303, 1290, 1197 cm^{-1}

NMR ($DMSO_6$, δ): 1.2–1.8 (18H, m), 3.3–3.9 (4H, m), 4.01 (2H, t, J=6.3Hz), 4.5–4.6 (1H, m), 7.03 (2H, d, J=8.7Hz), 7.67 (2H, d, J=8.7Hz), 7.74 (2H, d, J=8.3Hz), 7.98 (2H, d, J=8.3Hz)

APCI-MASS: m/z=425 ($M-H^+$)

Preparation 144

4-[3-(4-n-Hexyloxyphenyl)pyrazol-5-yl]benzoic acrylic acid

IR (KBr): 2956, 2935, 1693, 1614, 1508, 1432, 1251, 1178 cm^{-1}

NMR ($DMSO_6$, δ): 0.89 (3H, t, J=6.4Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 4.00 (2H, t, J=6.4Hz), 7.02 (2H, d, J=8.7Hz), 7.12 (1H, s), 7.74 (2H, d, J=8.7Hz), 7.95 (2H, d, J=8.8Hz), 8.01 (2H, d, J=8.8Hz), 13.17 (1H, s)

APCI-MASS: m/z=365 ($M+H^+$)

Preparation 145

4-[4-[4-(6-Methoxyhexyloxy)phenyl]phenyl]benzoic acid

IR (KBr): 2939, 2861, 1685, 1602, 1430, 1286, 1128 cm^{-1}

NMR ($DMSO_6$, δ): 1.3–1.8 (8H, m), 3.21 (3H, s), 3.3–3.4 (2H, m), 4.01 (2H, t, J=6.5Hz), 7.04 (2H, d, J=8.6Hz), 7.66 (2H, d, J=8.6Hz), 7.7–7.9 (6H, m), 8.03 (2H, d, J=8.2Hz)

APCI-MASS: m/z=405 ($M+H^+$)

Preparation 146

4-[5-[4-(8-Methoxyoctyloxy)phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid

IR (KBr): 2931, 2854, 1691, 1602, 1251 cm^{-1}

NMR ($DMSO_6$, δ): 1.2–2.0 (12H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4Hz), 4.04 (2H, d, J=6.4Hz), 7.13 (2H, t, J=8.8Hz), 7.9–8.2 (6H, m), 13.95 (1H, br)

APCI-MASS: m/z=441 ($M+H^+$)

Preparation 147

4-(4-n-Butoxyphenyl)cinnamic acid

IR (KBr): 2958, 2871, 1695, 1625, 1498, 1249 cm^{-1}

NMR ($DMSO_6$, δ): 0.94 (3H, t, J=7.3Hz), 1.44 (2H, tq, J=7.0 and 7.3Hz), 1.71 (2H, tt, J=7.0 and 6.4Hz), 4.01 (2H, t, J=6.4Hz), 6.54 (1H, d, J=16.0Hz), 7.02 (2H, d, J=8.7Hz), 7.6–7.9 (7H, m)

APCI-MASS: m/z=297 ($M+H^+$)

Preparation 148

4-[5-(4-Cyclohexylphenyl)-1,3,4-thiadiazol-2-yl] benzoic acid

IR (KBr): 2925, 2850, 1683, 1429, 1292 cm^{-1}

NMR ($DMSO_6$, δ): 1.1–1.5 (5H, m), 1.6–2.0 (5H, m), 2.4–2.6 (1H, m), 7.45 (2H, d, J=8.3Hz), 7.96 (2H, d, J=8.3Hz), 8.13 (4H, s)

APCI-MASS: m/z=365 ($M+H^+$)

Preparation 149

4-[5-[4-Piperidin-1-yl)phenyl]-1,3,4-thiadiazol-2-yl] benzoic acid

IR (KBr): 2931, 2854, 1685, 1604, 1415, 1238 cm^{-1}

NMR ($DMSO_6$, δ): 1.61 (6H, s), 3.31 (4H, s), 7.05 (2H, d, J=9.0Hz), 7.83 (2H, d, J=9.0Hz), 8.10 (4H, s)

APCI-MASS: m/z=366 $(M+H)^+$

Preparation 150

4-[5-[4-[4-n-Propyloxyphenyl)-phenyl]-1,3,4-oxadiazol-2-yl]benzoic acid

IR (KBr): 2939, 1689, 1606, 1488, 1429, 1290 cm^{-1}

NMR ($DMSO_6$, δ): 1.00 (3H, t, J=7.3Hz), 1.76 (2H, tq, J=6.5 and 7.3Hz), 4.00 (2H, t, J=6.5Hz), 7.07 (2H, d, J=8.8Hz), 7.70 (2H, d, J=8.5Hz), 7.78 (2H, d, J=8.8Hz), 7.90 (2H, d, J=8.5Hz), 8.0–8.4 (4H, m)

APCI-MASS: m/z=401 $(M+H)^+$

Preparation 151

4-(5-Nonyl-1,3,4-oxadiazol-2-yl)benzoic acid

IR (KBr): 2919, 2852, 1685, 1565, 1430, 1284 cm^{-1}

NMR ($DMSO_6$, δ): 0.84 (3H, t, J=6.5Hz), 1.2–1.5 (12H, m), 1.7–1.9 (2H, m), 2.94 (2H, t, J=7.4Hz), 8.0–8.2 (4H, m), 13.35 (1H, s)

APCI-MASS: m/z=317 $(M+H^+)$

Preparation 152

4-[5-(4-n-Hexyloxyphenyl)-1,2,4-oxadiazol-5-yl] benzoic acid

IR (KBr): 2942, 2869, 1695, 1421, 1251 cm^{-1}

NMR ($DMSO_6$, δ): 0.89 (3H, t, J=6.8Hz), 1.2–1.8 (8H, m), 4.06 (2H, t, J=6.5Hz), 7.13 (2H, d, J=8.9Hz), 8.03 (2H, d, J=8.9Hz), 8.17 (2H, d, J=8.5Hz), 8.28 (2H, d, J=8.5Hz)

APCI-MASS: m/z=367 $(M+H)^+$

Preparation 153

4-[4-[4-(5-Methoxypentyloxy)phenyl]phenyl] phenylacetic acid

IR (KBr): 2939, 2861, 1699, 1253, 1182, 1124 cm^{-1}

NMR ($DMSO_6$, δ): 1.4–1.9 (6H, m), 3.22 (3H, s), 3.39 (2H, t, J=6.2Hz), 3.61 (2H, s), 4.01 (2H, t, J=6.4Hz), 7.02 (2H, d, J=8.8Hz), 7.35 (2H, d, J=8.2Hz), 7.6–7.8 (8H, m)

APCI-MASS: m/z=405 $(M+H^+)$

Preparation 154

4-[5-(4-n-Octyloxyphenyl)-1,3,4-thiadiazol-2-yl] benzoic acid

IR (KBr): 2921, 2856, 1691, 1432, 1251 cm^{-1}

NMR ($DMSO_6$, δ): 0.87 (3H, t, J=6.7Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 4.07 (2H, t, J=6.5Hz), 7.13 (2H, d, J=8.9Hz), 7.97 (2H, d, J=8.9Hz), 8.12 (4H, s)

APCI-MASS: m/z=411 $(M+H^+)$

Preparation 155

4-[5-(4-Trans-n-pentylcyclohexyl)-1,3,4-thiadiazol-2-yl]benzoic acid

IR (KBr): 2919, 2848, 1677, 1430, 1294 cm^{-1}

NMR ($DMSO_6$, δ): 0.87 (3H, t, J=6.9Hz), 1.0–1.4 (11H, m), 1.5–1.6 (2H, m), 1.8–2.0 (2H, m), 2.1–2.3 (2H, m), 3.1–3.3 (1H, m), 8.07 (4H, s)

APCI-MASS: m/z=359 $(M+H^+)$

Preparation 156

4-[3-(4-n-Pentyloxyphenyl)isoxazol-5-yl]benzoic acid

IR (KBr): 2925, 2869, 1699, 1687, 1612, 1432, 1251, 1178 cm^{-1}

NMR ($DMSO_6$, δ): 0.91 (3H, t, J=6.9Hz), 1.2–1.5 (4H, m), 1.7–1.9 (2H, m), 4.04 (2H, t, J=6.5Hz), 7.09 (2H, d, J=8.8Hz), 7.69 (1H, s), 7.85 (2H, d), J=8.8Hz), 8.01 (2H, d, J=8.5Hz), 8.11 (2H, d, J=8.5Hz)

APCI-MASS: m/z=352 $(M+H^+)$

Preparation 157

4-[5-[4-(8-Methoxyoctyloxy)phenyl]-1,3,4-oxadiazol-2-yl]benzoic acid

IR (KBr): 2967, 2937, 2877, 1687, 1290 cm^{-1}

NMR ($DMSO_6$, δ): 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4Hz), 4.08 (2H, t, J=6.5Hz), 7.17 (2H, d, J=8.9Hz), 8.07 (2H, d, J=8.9Hz), 8.15 (2H, d, J=8.6Hz), 8.24 (2H, d, J=8.6Hz)

APCI-MASS: m/z=425 $(M+H)^+$

Preparation 158

4-[4-(6-Phenylpyridazin-3-yl-oxy)phenyl]benzoic acid

IR (KBr): 1700, 1687, 1608, 1427, 1284, 1186 cm^{-1}

NMR ($DMSO_6$, δ): 7.40 (2H, d, J=8.6Hz), 7.5–7.7 (4H, m), 7.7–7.9 (4H, m), 7.9–8.1 (4H, m), 8.35 (1H, d, J=9.2Hz), 12.99 (1H, br s)

APCI-MASS: m/z=369 $(M+H)^+$

Preparation 159

4-[5-(4-n-Octyloxyphenyl)-1,3,4-oxadiazol-2-yl] benzoic acid

IR (KBr): 2921, 2852, 1685, 1612, 1496, 1425, 1288, 1251 cm^{-1}

NMR ($DMSO_6$, δ): 0.87 (3H, t, J=6.7Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 4.08 (2H, t, J=6.4Hz), 7.17 (2H, d, J=8.7Hz), 8.07 (2H, d, J=8.7Hz), 8.15 (2H, d, J=8.5Hz), 8.24 (2H, d, J=8.5Hz), 13.36 (1H, br)

APCI-MASS: m/z=395 $(M+H^+)$

Preparation 160

4-[2-(4-n-Hexyloxyphenyl)pyrimidin-6-yl]benzoic acid

IR (KBr): 2944, 2863, 1697, 1585, 1415, 1386, 1253 cm^{-1}

NMR ($DMSO_6$, δ): 0.89 (3H, t, J=6.7Hz), 1.2–1.6 (6H, m), 1.7–1.9 (2H, m), 4.07 (2H, t, J=6.6Hz), 7.10 (2H, d, J=8.9Hz), 8.00 (1H, d, J=5.2Hz), 8.13 (2H, d, J=8.4Hz), 8.44 (2H, d, J=5.9Hz), 8.47 (2H, d, J=5.9Hz), 8.95 (1H, d, J=5.2Hz)

APCI-MASS: m/z=377 $(M+H^+)$

Preparation 161

4-[4-(7-Piperidinocarbonylheptyloxy)phenyl]benzoic acid

IR (KBr): 2933, 2858, 1697, 1677, 1637, 1604, 1429, 1249 cm^{-1}

NMR ($DMSO_6$, δ): 1.2–1.8 (16H, m), 2.26 (2H, t, J≦7.5Hz), 3.2–3.5 (4H, m), 4.01 (2H, t, J=6.4Hz), 7.03 (2H, d, J=8.8Hz), 7.67 (2H, d, J=8.8Hz), 7.74 (2H, d, J=8.4Hz) 7.98 (2H, d, J=8.4Hz)

APCI-MASS: m/z=424 ($M+H^+$)

Preparation 162

6-[4-(4-n-Heptyloxyphenyl)-piperazin-1-yl]nicotinic acid

IR (KBr): 2929, 2854, 1695, 1673, 1606, 1577, 1515, 1421 1245 cm^{-1}

NMR ($DMSO_6$, δ): 0.86 (3H, t, J=6.7Hz), 1.2–1.5 (8H, m), 1.6–1.8 (2H, m), 3.0–3.2 (4H, m), 3.6–3.8 (4H, m), 3.87 (2H, t, J=6.5Hz), 6.8–7.2 (5H, m), 7.95 (1H, dd, J=8.9 and 2.3 Hz), 8.62 (1H, d, J=2.3 Hz) APCI-MASS: m/z=398 ($M+H^+$)

Preparation 163

6-[4-[4-(8-Methoxyoctyloxy)phenyl]piperazin-1-yl]-nicotinic Acid

IR (KBr): 2933, 856, 1697, 1672, 1605, 1511, 1421, 1245 cm^{-1} NMR (DMSO-d_6, δ): 1.2–1.8 (12H, m), 3.08 (4H, t, J=5.0 Hz), 3.20 (3H, s), 3.28 (2H, t, J=6.5 Hz), 3.78 (4H, t, J=4.6 Hz), 3.87 (2H, t, J=6.4 Hz), 6.8–7.0 (5H, m), 7.95 (1H, dd, J=9.0 and 2.2 Hz), 8.65 (1H, d, J=2.2 Hz), 12.54 (1H, s) APCI-MASS: m/z=442 ($M+H^+$)

Preparation 164

4-[5-[4-(4-n-Propyloxyphenyl)phenyl]-1,3,4-thiadiazol-2-yl]benzoic Acid

IR (KBr): 1685, 1537, 1423, 817 cm^{-1} NMR (DMSO-d_6, δ): 1.00 (3H, t, J=6.7 Hz), 1.6–1.8 (2H, m), 4.00 (2H, t, J=6.6 Hz), 7.0–7.2 (2H, d, J=8.6 Hz), 7.6–8.1 (10H, m)

APCI-MASS: m/z=417 $(M+H)^+$

Preparation 165

To a solution of Ethyl 4-[5-(4-n-pentyloxyphenyl)-isoxazol-3-yl]benzoate (6.33 g) in ethanol (60 ml) and tetrahydrofuran (90 ml) was added 2N sodium hydroxide aqueous solution (12.5 ml) at 80° C. The mixture was refluxed for 1 hour and poured into ice-water. The suspension was adjusted to pH 2.0 with 1N HCl. The precipitate was collected by filtration, washed with water and dried to give 4-[5-(4-n-pentyloxyphenyl)isoxazol-3-yl]benzoic acid (5.80 g).

IR (KBr): 2939, 2867, 1681, 1614, 1429, 1255, 1178, 821 cm^{-1} NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.1 Hz), 1.3–1.5 (4H, m), 1.6–1.8 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.11 (2H, d, J=8.9 Hz), 7.54 (1H, s), 7.85 (2H, d, J=8.9 Hz), 7.98 (2H, d, J=8.6 Hz), 8.11 (2H, d, J=8.6 Hz) APCI-MASS: m/z=352 $(M+H)^+$

The following compounds (Preparation 166 to 170) were obtained according to a similar manner to that of Preparation 40.

Preparation 166

5-[4-(4-n-Hexyloxphenyl)piperazin-1-yl]picolic Acid Trihydrochloride

IR (KBr): 1689.3, 1577.5, 1511.9, 1241.9 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.5 Hz), 1.15–1.5 (6H, m), 1.6–1.8 (2H, m), 3.1–3.25 (4H, m), 3.45–3.6 (4H, m), 3.89 (2H, t, J=6.4 Hz), 6.84 (2H, d, J=9.1 Hz), 6.97 (2H, d, J=9.1 Hz), 7.43 (1H, dd, J=8.8 and 3.0 Hz), 7.90 (1H, dd, J=8.8 and 0.7 Hz), 8.41 (1H, dd, J=3.0 and 0.7 Hz) APCI-MASS: m/z=384 (M^++H)

Preparation 167

4-[4-(4-Phenylcyclohexyl)piperazin-1-yl]benzoic Acid Dihydrochloride

IR (KBr): 1700.9, 1606.4, 1220.7, 1180.2 cm^{-1} NMR (DMSO-d_6, δ): 1.4–1.85 (4H, m), 1.9–2.05 (2H, m), 2.2–2.4 (2H, m), 3.1–3.5 (6H, m), 3.5–3.7 (2H, m), 3.9–4.2 (2H, m), 7.06 (2H, d, J=8.8 Hz), 7.1–7.4 (5H, m), 7.83 (2H, d, J=8.8 Hz) APCI-MASS: m/z=365 (M^++H)

Preparation 168

4-(4-Trans-n-pentylcyclohexyl)benzoic Acid

IR (KBr): 1681.6, 1423.2, 1290.1 cm^{-1} NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.6 Hz), 1.0–1.6 (13H, m), 1.89 (4H, d, J=10 Hz), 2.54 (1H, t, J=12 Hz), 7.30 (2H, d, J=8.3 Hz), 8.03 (2H, d, J=8.3 Hz) APCI-MASS: m/z=274 (M^++H)

Preparation 169

4-(4-Piperidinopiperidin-1yl)benzoic Acid

IR (KBr): 1710.6, 1403.9 cm^{-1} NMR (DMSO-d_6, δ): 1.6–2.1 (8H, m), 2.17 (2H, d, J=12 Hz), 2.7–3.05 (4H, m), 3.2–3.5 (1H, m), 3.35 (2H, d, J=12 Hz), 4.05 (2H, d, J=13 Hz), 7.01 (2H, d, J=8.9 Hz), 7.77 (2H, d, J=8.9 Hz), 10.84 (1H, s) APCI-MASS: m/z=289 (M^++H)

Preparation 170

3-Chloro-4-[4-(4-n-hexyloxyphenyl)piperazin-1-yl]benzoic Acid Dihydrochloride

IR (KBr): 1712.5, 1598.7, 1513.8, 1251.6 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 3.4–3.6 (8H, m), 3.98 (2H, t, J=6.4 Hz), 7.02 (2H, d, J=9.0 Hz), 7.32 (1H, d, J=8.1 Hz), 7.60 (2H, d, J=9.0 Hz), 7.89 (1H, d, J=8.1 Hz), 8.02 (1H, s) APCI-MASS: m/z=417 (M^++H)

The following compounds (Preparations 171 to 175) were obtained according to a similar manner to that of Preparation 41.

Preparation 171

Ethyl [4-(4-octylphenyl)-2,3-dihydro-4H-1,2,4-triazole-3-one-2yl]acetate

IR (KBr): 1921.6, 1764.5, 1715, 1197.6 cm^{-1} NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.7 Hz), 1.30 (3H, t, J=7.1 Hz), 1.2–1.4 (10H, m), 1.5–1.7 (2H, m), 2.63 (2H, t, J=7.9 Hz), 4.26 (2H, q, J=7.1 Hz), 4.64 (2H, s), 7.28 (2H, d, J=8.4 Hz), 7.44 (2H, d, J=8.4 Hz), 7.71 (1H, s)

Preparation 172

4-[4-(4-tert-Butoxycarbonylpiperazin-1-yl)phenyl]-2(4-methylpentyl)-2,3-dihydro-4H-1,2,4-triazol-3-one

IR (KBr): 1687.4 cm^{-1} NMR ($CDCl_3$, δ): 0.90 (6H, d, J=6.5 Hz), 1.1–1.4 (2H, m), 1.49 (9H, s), 1.4–1.9 (3H, m), 3.16 (4H, t, J=4.9 Hz), 3.59 (4H, t, J=4.9 Hz), 3.82 (2H, t, J=7.3 Hz), 6.98 (2H, d, J=9.0 Hz), 7.41 (2H, d, J=9.0 Hz), 7.61 (1H, s)

Preparation 173

Methyl 6-(8-bromooctyloxy)-2-naphthoate

IR (KBr): 2933.2, 2856.1, 1720.2, 1294, 1209.1 cm^{-1} NMR ($CDCl_3$, δ): 1.3–1.6 (8H, m), 1.75–2.0 (4H, m), 3.42 (2H, t, J=6.8 Hz), 3.96 (3H, s), 4.09 (2H, t, J=6.5 Hz), 7.14 (1H, d, J=1.7 Hz), 7.19 (1H, dd, J=8.9 and 1.7 Hz, 7.73 (1H, d, J=8.7 Hz), 7.83 (1H, d, J=8.9 Hz), 8.01 (1H, dd, J=8.7 and 1.7 Hz), 8.51 (1H, d, J=1.7 Hz) APCI-MASS: m/z=393 (M^++H)

Preparation 174

4-[4-(6-n-Propyloxyphenyl)phenyl]benzoic Acid

IR (KBr): 2937, 2858, 1695, 1683, 1604, 1430, 1290, 1247, 1195 cm^{-1} NMR (DMSO-d_6, δ): 0.85 (3H, t, J=7.4

Hz), 1.3–1.9 (10H, m), 3.2–3.4 (4H, m), 4.01 (2H, t, J=6.3 Hz), 7.04 (2H, d, J=8.7 Hz), 7.67 (2H, d, J=8.7 Hz), 7.74 (2H, d, J=8.3 Hz), 7.98 (2H, d, J=8.3 Hz), 12.9 (1H, APCI-MASS: m/z=357 ($M+H^+$)

Preparation 175

4-[4-(6-Bromohexyloxy)phenyl]bromobenzene

NMR ($CDCl_3$, δ): 1.40–1.65 (4H, m), 1.70–2.00 (4H, m), 3.43 (2H, t, J=6.7 Hz), 4.00 (2H, t, J=6.4 Hz), 6.95 (2H, d, J=8.8 Hz), 7.30–7.60 (6H, m)

The following compounds (Preparations 176 to 180) were obtained according to a similar manner to that of Preparation 43.

Preparation 176

4-[4-(4-n-Pentyloxyphenyl)piperazin-1-yl]benzoic Acid Dihydrochloride

IR (KBr): 1668.1, 1602.6, 1510.0, 1228.4 cm^{-1} NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.9 Hz), 1.2–1.5 (5H, m), 1.6–1.9 (2H, m), 3.0–3.2 (4H, m), 3.4–3.6 (4H, m), 3.88 (2H, t, J=6.4 Hz), 6.83 (2H, d, J=9 Hz), 6.9–7.1 (4H, m), 7.79 (2H, d, J=8.8 Hz), 12.32 (1H, s) APCI-MASS: m/z=369 ($M+H^+$)

Preparation 177

4-[4-(4-n-Heptyloxyphenyl)piperazin-1-yl]benzoic Acid Dihydrochloride

IR (KBr): 1666.2, 1600.6, 1511.9 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.9 Hz), 1.2–2.0 (10H, m), 3.1–3.3 (4H, m), 3.4–3.6 (4H, m), 3.92 (2H, t, J=6.4 Hz), 6.8–7.1 (6H, m), 8.00 (2H, d, J=8.8 Hz)

Preparation 178

4-[4-[4-(4-Methylpentyloxy)phenyl]piperazin-1-yl]benzoic Acid Hydrochloride

IR (KBr): 1668.1, 1602.6, 1510.0, 1236.1 cm^{-1} NMR (DMSO-d_6, δ): 0.89 (6H, d, J=6.5 Hz), 1.2–1.4 (2H, m), 1.4–1.8 (3H, m), 3.0–3.2 (4H, m), 3.3–3.5 (4H, m), 3.87 (2H, t, J=6.3 Hz), 6.83 (2H, d, J=9.0 Hz), 6.9–7.1 (4H, m), 7.79 (2H, d, J=8.8 Hz), 12.33 (1H, s) APCI-MASS: m/z=383 ($M+H^+$)

Preparation 179

4-[4-[4-(8-Bromooctyloxy)phenyl]piperazin-1-yl]benzoic Acid Dihydrochloride

IR (KBr): 1670.1, 1602.6, 1511.9, 1234.2 cm^{-1} NMR (DMSO-d_6, δ): 1.2–1.5 (8H, m), 1.6–1.9 (4H, m), 3.0–3.2 (4H, m), 3.2–3.5 (4H, m), 3.52 (2H, t, J=6.7 Hz), 3.88 (2H, t, J=6.4 Hz), 6.83 (2H, d, J=9.1 Hz), 6.94 (2H, d, J=9.1 Hz), 7.02 (2H, d, J=8.9 Hz), 7.79 (2H, d, J=8.9 Hz)

Preparation 180

3-Fluoro-4-[4-(4-n-hexyloxyphenyl)piperazin-1yl]benzoic Acid Dihydrochloride

IR (KBr): 1673.9, 1511.9, 1240.0 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.5 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 3.0–3.5 (8H, m), 3.88 (2H, t, J=6.4 Hz), 6.7–7.2 (5H, m), 7.4–7.8 (2H, m), 12.82 (1H, s) APCI-MASS: m/z=401 (M^++H)

The following compound was obtained according to a similar manner to that of Preparation 46.

Preparation 181

1-(4-Methoxycarbonylphenyl)-3-(4-n-hexyloxyphenyl)-propan-1,3-dione

IR KBr: 2956, 2927, 2856, 1722, 1511, 1284, 1108 cm^{-1} NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.4 Hz), 1.2–2.0 (8H, m), 3.96 (3H, s), 4.04 (2H, t, J=6.5 Hz), 6.82 (1H, s), 6.97 (2H, d, J=8.7 Hz), 7.9–8.1 (4H, m), 8.14 (2H, d, J=8.3 Hz) APCI-MASS: m/z=383 ($M+H^+$)

The following compounds (Preparations 182 to 185) were obtained according to a similar manner to that of Preparation 47.

Preparation 182

Methyl 5-(4-octyloxyphenyl)-1-methylpyrazole-3-carboxylate

IR (KBr pelet): 2923, 1724, 1616, 1513, 1446, 1251, 1120 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 3.90 (3H, s), 3.98 (2H, t, J=6.6 Hz), 4.20 (3H, s), 6.92 (2H, d, J=8.9 Hz), 7.04 (1H, s), 7.89 (2H, d, J=8.9 Hz) APCI-MASS: m/z=345 ($M+H^+$)

Preparation 183

Methyl 4-[5-(4-n-pentyloxyphenyl)pyrazol-3-yl]benzoate

IR (KBr): 3236, 2952, 2873, 1716, 1616, 1508, 1276, 1174, 1106 cm^{-1} NMR ($CDCl_3$, δ): 0.94 (3H, t, J=7.0 Hz), 1.3–1.5 (4H, m), 1.7–1.9 (2H, m), 3.92 (3H, s), 3.96 (2H, t, J=6.7 Hz), 6.78 (1H, s), 6.88 (2H, d, J=8.7 Hz), 7.55 (2H, d, J=8.7 Hz), 7.79 (2H, d, J=8.4 Hz), 8.02 (2H, d, J=8.4 Hz) APCI-MASS: m/s=365 ($M+H^+$)

Preparation 184

Methyl 5-(4-octyloxyphenyl)isoxazole-3-carboxylate

IR (KBr pelet): 2950, 2921, 1724, 1614, 1510, 1446, 1257, 1178, 1143, 1009 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 4.0–4.1 (5H, m), 6.80 (1H, s), 6.98 (2H, dd, J=6.9 and 2.1 Hz), 7.73 (2H, dd,, J=6.9 and 2.1 Hz) APCI-MASS: m/z=332 ($M+H^+$)

Preparation 185

Methyl 4-[3-(4n-hexyloxyphenyl)pyrazol-5-yl]benzoate

IR (KBr): 2952, 1716, 1616, 1508, 1276, 1106 cm^{-1} NMR ($CDCl_3$, δ): 0.91 (3H, T, J=6.3 Hz), 1.2–1.6 (6H, m), 1.7–1.9 (2H, m), 3.8–4.0 (5H, m), 6.76 (1H, s), 6.86 (2H, d, J=8.8 Hz), 7.54 (2H, d, =8.8 Hz), 7.77 (2H, d, J=8.4 Hz), 8.00 (2H, d, J=8.4 Hz) APCI-MASS: m/z=379 ($M+H^+$)

Preparation 186

A suspension of 1-(4-n-Pentyloxyphenyl)-3-(4-ethoxycarbonylphenyl)-1-buten-3-one (74.43 g) and hydroxyamine hydrochloride (28.23 g) and potassium carbonate (56.11 g) in ethanol (400 ml) was refluxed for 4 hours. The mixture was diluted with ethyl acetate, washed with water (×2), brine and dried over magnesium sulfate. The solvents were removed under reduced pressure to give crude oxime. To a solution of crude oxime in dichloroethane (500 ml) was added activated-manganese (IV) oxide (200 g). The reaction mixture was refluxed for 2 hours and filtered. The residue was washed with dichloromethane. The solvents were removed under reduced pressure and the residue was triturated with acetonitrile. The solid was collected by filtration and dried to give the ethyl 4-[5-(4-n-Pentyloxyphenyl)isoxazol-3-yl]benzoate (21.07 g).

IR (KBr): 2945, 2872, 1717, 1615, 1508, 1280, 1108 cm^{-1} NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.9 Hz), 1.3–1.9 (9H, m), 4.01 (2H, t, J=6.5 Hz), 4.41 (2H, q, J=7.1 Hz), 6.74 (1H, s), 6.99 (2H, d, J=8.8 Hz), 7.76 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.4 Hz), 8.15 (2H, d, J=8.4 Hz) APCI-MASS: m/z=380 ($M+H^+$)

The following compounds (Preparations 187 to 190) were obtained according to a similar manner to that of Preparation 48.

Preparation 187

Methyl 6-[4-[4-(8-Methoxyoctyloxy)phenyl]piperazin-1-yl] nicotinate

IR (KBr): 2933, 2858, 1722, 1608, 1513, 1432, 1405, 1278, 1245 cm^{-1} NMR ($CDCl_3$, δ): 1.3–1.9 (12H, m), 3.16 (4H, t, J=5.0 Hz), 3.33 (3H, s), 3.36 (2H, t, J=6.5 Hz), 3.8–4.0 (9H, m), 6.64 (1H, d, J=9.1 Hz), 6.85 (2H, d, J=9.2 Hz), 6.93 (2H, d, J=9.2 Hz), 8.04 (1H, dd, J=9.1 and 2.2 Hz), 8.81 (1H, d, J=2.2 Hz) APCI-MASS: m/z=456 ($M+H^+$)

Preparation 188

4-[4-(5-methoxypentyloxy)phenyl]bromobenzene

IR (KBr): 2940, 2856, 1604, 1479, 1286, 1255, 1124 cm^{-1} NMR ($CDCl_3$, δ): 1.5–1.9 (6H, m), 3.34 (3H, s), 3.41 (2H, t, J=6.1 Hz), 3.99 (2H, t, J=6.4 Hz), 6.95 (2H, d, J=8.7 Hz), 7.4–7.6 (6H, m) APCI-MASS: m/z=349 ($M+H^+$)

Preparation 189

Methyl 6-(8-methoxyoctyloxy)-2-naphthoate NMR (DMSO-d_6, δ): 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.89 (3H, s), 4.11 (2H, t, J=6.4 Hz), 7.24 (1H, dd, J=9.0 and 2.4 Hz), 7.40 (1H, d, J=2.4 Hz), 7.88 (1H, d, J=8.7 Hz), 7.94 (1H, dd, J=8.7 and 1.5 Hz), 8.03 (1H, d, J=9.0 Hz), 8.55 (1H, d, J=1.5 Hz)

Preparation 190

4-[4-[4-(8-Methoxyoctyloxy)phenyl]piperazin-1yl]benzoic Acid Dihydrochloride

IR (KBr): 1668.1, 1602.6, 1511.9, 1236.1 cm^{-1} NMR (DMSO-d_6, δ): 1.2–1.8 (12H, m), 3.05–3.2 (4H, m), 3.29 (2H, t, J=7.1 Hz), 3.33 (3H, s), 3.4–3.55 (4H, m), 3.88 (2H, t, J=6.4 Hz), 6.82 (2H, d, J=9.0 Hz), 6.94 (2H, d, J=9.0 Hz), 7.02 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.8 Hz), 12.31 (1H, s)

The following compounds (Preparations 191 to 254) were obtained according to a similar manner to that of Preparation 49.

Preparation 191

1-[4-[4-[4-[2-(4-Methylpentyl)-2,3-dihydro-4H, 1,2,4-triazol-3-one-4-yl]phenyl]piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1766.5, 1693.2, 1600.6, 1519.6 cm^{-1}

Preparation 192

1-[4-(4-Octylphenyl)-2,3-dihydro-4H-1,2,4-triazol-3one-2-yl-acetyl]benzotriazole 3-oxide

IR (KBr): 2921.6, 1753.0, 1720.0, 1423.2 cm^{-1} NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.7 Hz), 1.2–1.4 (10H, m), 1.5–1.8 (2H, m), 2.65 (2H, t, J=7.5 Hz), 5.46 (2H, s), 7.30 (2H, d, J=8.5 Hz), 7.48 (2H, d, J=8.5 Hz), 7.62 (1H, t, J=8.3 Hz), 7.80 (1H, s), 7.82 (1H, t, J=8.3 Hz), 8.05 (1H, d, J=8.3 Hz), 8.37 (1H, d, J=8.3 Hz)

Preparation 193

1-[4-[4-[4-(7-Methoxyheptyloxy)phenyl]piperazin-1-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 1783.8, 1600.6, 1511.9, 1232.3, 1184.1 cm^{-1} NMR ($CDCl_3$, δ): 1.3–1.9 (10H, m), 3.2–3.3 (4H, m), 3.34 (3H, s), 3.38 (2H, t, J=6.4 Hz), 3.5–3.7 (4H, m), 3.92 (2H, t, J=6.5 Hz), 6.87 (2H, d, J=9.2 Hz), 6.95 (2H, d, J=9.2 Hz), 7.00 (2H, d, J=9.0 Hz), 7.3–7.6 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.0 Hz)

Preparation 194

1-[4-[4-(4-n-Heptyloxyphenyl)piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1783.8, 1600.6, 1511.9, 1230.4, 1184.1 cm^{-1} NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.3 Hz), 1.2–1.6 (8H, m), 1.7–1.9 (2H, m), 3.2–3.3 (4H, m), 3.5–3.7 (4H, m), 3.93 (2H, t, J=6.5 Hz), 6.87 (2H, d, J=9.2 Hz), 6.95 (2H, d, J=9.2 Hz), 7.00 (2H, d, J=9.0 Hz), 7.3–7.7 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.0 Hz)

Preparation 195

1-[4-[4-[4-(4-Methylpentyloxy)phenyl]piperazin-1-yl] benzoyl]benzotriazole 3-oxide

NMR ($CDCl_3$, δ): 0.92 (6H, d, J=6.6 Hz), 1.2–1.4 (2H, m), 1.5–1.9 (3H, m), 3.1–3.3 (4H, m), 3.5–3.7 (4H, m), 3.92 (2H, t, J=6.6 Hz), 6.87 (2H, d, J=9.3 Hz), 6.96 (2H, d, J=9.3 Hz), 7.01 (2H, d, J=9.0 Hz), 7.4–7.6 (3H, m), 8.10 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.0 Hz)

Preparation 196

1-[4-[4-(4-n-Pentyloxyphenyl)piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1787.7, 1600.6, 1511.9, 1232.3, 1184.1 cm^{-1} NMR ($CDCl_3$, δ): 0.93 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.7–1.9 (2H, m), 3.1–3.4 (4H, m), 3.5–3.8 (4H, m), 3.93 (2H, t, J=6.6 Hz), 6.87 (2H, d, J=9.2 Hz), 6.92 (2H, d, J=9.2 Hz), 7.01 (2H, d, J=9.1 Hz), 7.4–7.6 (3H, m), 8.10 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.1 Hz)

Preparation 197

1-[4-[4-[8-(1H-Tetrazol-1-yl)octyloxy]phenyl]benzoyl] benzotriazole 3-oxide and 1-[4-[4-[8-(2H-tetrazol-2-yl) octyloxy]phenyl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1778.0, 1602.6, 1189.9, 981.6 cm^{-1} NMR ($CDCl_3$, δ): 1.2–1.6 (8H, m), 1.7–1.9 (2H, m), 1.9–2.2 (2H, m), 4.02 (2H, t, J=6.4 Hz), 4.44 and 4.66 (2H, t, J=7.1 Hz), 7.02 (2H, d, J=8.8 Hz), 7.4–7.6 (3H, m), 7.63 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.6 Hz), 8.12 (1H, d, J=8.2 Hz), 8.32 (2H, d, J=8.6 Hz), 8.51 and 8.60 (1H, s)

Preparation 198

1-[4-[4-[8-(2,6-Dimethylmorpholin-4-yl)octyloxy]phenyl] benzoyl]benzotriazole 3-oxide

IR (KBr): 1778.0, 1600.6, 977.7 cm^{-1} NMR ($CDCl_3$, δ): 1.18 (6H, d, J=6.3 Hz), 1.2–1.7 (10H, m), 1.7–2.0 (4H, m), 2.4–2.6 (2H, m), 2.9–3.2 (2H, m), 3.7–3.9 (2H, m), 4.01 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.8 Hz), 7.4–7.7 (3H, m), 7.63 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.5 Hz), 8.12 (1H, d, J=8.1 Hz), 8.32 (2H, d, J=8.5 Hz)

Preparation 199

1-[6-[4-(4-Octyloxyphenyl)piperazin-1-yl]nicotinoyl] benzotriazole 3-oxide

IR (KBr pelet): 2922, 2854, 1766, 1602, 1513, 1417, 1234, 1025, 950, 813 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 3.1–3.3 (4H, m), 3.9–4.1 (6H, m), 6.75 (1H, d, J=9.2 Hz), 6.87 (2H, d, J=9.2 Hz), 6.95 (2H, d, J=9.2 Hz), 7.4–7.6 (3H, m), 8.10 (1H, d, J=8.1 Hz), 8.19 (1H, dd, J=9.2 and 2.4 Hz), 9.04 (1H, d, J=2.4 Hz) APCI-MASS: m/z=529 ($M+H^+$)

Preparation 200

1-[2-(4-Hexyloxyphenyl)benzoxazol-5-yl-carbonyl] benzotriazole 3-oxide

IR (KBr): 2950, 1774, 1623, 1504, 1265, 1176 cm^{-1} NMR ($CDCl_3$, δ): 0.93 (3H, t, J=6.9 Hz), 1.3–1.6 (6H, m), 1.8–2.0 (2H, m), 4.07 (2H, t, J=6.5 Hz), 7.06 (2H, d, J=8.9 Hz), 7.4–7.6 (3H, m), 7.75 (1H, d, J=8.6 Hz), 8.13 (1H, d, J=8.2 Hz), 8.2–8.4 (3H, m), 8.67 (1H, d, =1.6 Hz) APCI-MASS: m/z=457 ($M+H^+$)

Preparation 201

1-[4-[4-(4-n-Butyloxyphenyl)phenyl]benzoyl]benzotriazole 3-oxide

IR (KBr): 2958, 2871, 1776, 1600, 1398, 1255, 1211, 1037 cm^{-1} NMR ($CDCl_3$, δ): 1.00 (3H, t, J=7.2 Hz), 1.4–1.9 (4H, m), 4.03 (2H, t, J=6.4 Hz), 7.01 (2H, d, J=8.3 Hz), 7.4–7.8 (9H, m), 7.87 (2H, d, J=8.1 Hz), 8.12 (1H, d, J=8.4 Hz), 8.36 (2H, d, J=7.9 Hz) APCI-MASS: m/z=464 $(M+H)^+$

Preparation 202

1-[2-(4-Heptyloxyphenyl)pyridin-5-yl-carbonyl] benzotriazole 3-oxide

IR (KBr): 2944, 2867, 1793, 1770, 1589, 1471, 1321, 1093 cm^{-1} NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.7 Hz), 1.2–1.6 (8H, m), 1.7–1.9 (2H, m), 4.05 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.0 Hz), 7.4–7.6 (3H, m), 7.91 (1H, d, J=8.5 Hz), 8.1–8.2 (3H, m), 8.51 (1H, dd, J=8.5 and 2.3 Hz), 9.47 (1H, d, J=2.3 Hz) APCI-MASS: m/z=431 $(M+M^+)$

Preparation 203

1-[2-(2-Octyloxypyridin-5-yl)benzoxazol-5-yl-carbonyl] benzotriazole 3-oxide

IR (KBr pelet): 2925, 2854, 1787, 1623, 1479, 1263, 989 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.8–1.9 (2H, m), 4.42 (2H, t, J=6.7 Hz), 6.91 (1H, d, J=8.7 Hz), 6.4–6.6 (3H, m), 7.79 (1H, d, J=8.6 Hz), 8.13 (1H, d, J=8.2 Hz), 8.32 (1H, dd, J=8.6 and 1.7 Hz), 8.41 (1H, dd, J=8.7 and 2.4 Hz), 8.70 (1H, d, J=1.4 Hz), 9.07 (1H, d, J=1.9 Hz) APCI-MASS: m/z=486 $(M+H^+)$

Preparation 204

1-[2-[4-(4-Hexylphenyl)phenyl]benzoxazol-5-yl-carbonyl] benzotriazole 3-oxide

IR (KBr): 2927, 2854, 1785, 1621, 1490, 1261, 1166, 1052 cm^{-1} NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.8 (8H, m), 2.68 (2H, t, J=7.9 Hz), 7.31 (2H, d, J=8.2 Hz), 7.4–7.7 (5H, m), 7.79–7.81 (3H, m), 8.13 (1H, d, J=8.3 Hz), 8.3–8.4 (3H, m), 8.73 (1H, d, J=1.3 Hz) APCI-MASS: m/z=517 $(M+H^+)$

Preparation 205

1-[2-[4-(4-n-Butyloxyphenyl)phenyl]pyridin-5-yl-carbonyl] benzotriazole 3-oxide

IR (KBr): 2956, 2933, 2871, 1774, 1650, 1591, 1471, 1251 cm^{-1} NMR ($CDCl_3$, δ): 1.00 (3H, t, J=7.2 Hz), 1.5–1.9 (4H, m), 4.03 (2H, t, J=6.4 Hz), 7.02 (2H, d, J=8.6 Hz), 7.4–7.6 (3H, m), 7.54 (2H, d, J=7.3 Hz), 7.62 (2H, d, J=8.5 Hz), 8.02 (1H, d, J=8.3 Hz), 8.13 (1H, d, J=8.2 Hz), 8.21 (2H, d, J=7.9 Hz), 8.57 (1H, dd, J=8.3 and 2.0 Hz), 9.54 (1H, d, J=2.0 Hz) APCI-MASS: m/z=465 $(M+H)^+$

Preparation 206

1-[4-[4-(5-Phenoxypentyloxy)phenyl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2944, 2869, 1770, 1600, 1494, 1249, 1189 cm^{-1} NMR ($CDCl_3$, δ): 1.6–1.8 (2H, m), 1.8–2.0 (4H, m), 4.01 (2H, t, J=6.3 Hz), 4.07 (2H, t, J=6.2 Hz), 6.91 (2H, d, J=8.9 Hz), 7.04 (2H, d, J=8 .7 Hz), 7.3–7.6 (4H, m), 7.63 (2H, d, J=8.6 Hz), 7.78 (2H, d, J=8.4 Hz), 8.12 (1H, d, J=8.1 Hz), 8.32 (2H, d, J=8.4 Hz) APCI-MASS: m/z=494 $(M+H)^+$

Preparation 207

1-[4-[5-(4-Hexyloxyphenyl)-1,3,4-oxadiazol-2-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2956, 2921, 2856, 1778, 1612, 1496, 1261, 1232, 1025 cm^{-1} NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.7 Hz), 1.3–1.6 (6H, m), 1.8–2.0 (2H, m), 4.05 (2H, t, J=6.5 Hz), 7.05 (2H, d, J=8.7 Hz), 7.4–7.6 (3H, m), 8.10 (2H, d, J=8.7 Hz), 8.13 (1H, d, J=7.4 Hz), 8.37 (2H, d, J=8.5 Hz), 8.45 (2H, d, J=8.5 Hz) APCI-MASS: m/z=494 $(M+H)^+$

Preparation 208

1-[4-[5-(4-n-Hexyloxyphenyl)-1,3,4-thiadiazol-2-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2952, 2873, 1774, 1602, 1261, 1230, 1176 cm^{-1} NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.8 Hz), 1.3–2.0 (8H, m), 4.04 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.7 Hz), 7.4–7.7 (3H, m), 7.98 (2H, d, J=8.7 Hz), 8.13 (1H, d, J=8.7 Hz), 8.25 (2H, d, J=8.3 Hz), 8.41 (2H, d, J=8.3 Hz) APCI-MASS: m/z=500 $(M+H)^+$

Preparation 209

1-[5-(4-Octyloxyphenyl)-1-methylpyrazol-3-yl-carbonyl] benzotriazole 3-oxide

IR (KBr pelet): 2939, 2852, 1776, 1687, 1612, 1448, 1249, 995 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.3–1.5 (10H, m), 1.7–1.9 (2H, m), 4.01 (2H, t, J=6.5 Hz), 4.25 (3H, s), 6.97 (2H, d, J=6.8 Hz), 7.4–7.7 (4H, m), 7.78 (2H, d, J=6.8 Hz), 8.14 (1H, d, J=8.0 Hz) APCI-MASS: m/z=448 $(M+H^+)$

Preparation 210

1-[4-[5-(4-n-Pentyloxyphenyl)pyrazol-3-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 3251, 2956, 2869, 1780, 1612, 1506, 1232, 985 cm^{-1} NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.7–2.0 (2H, m), 4.01 (2H, t, J=6.6 Hz), 6.90 (1H, s), 6.99 (2H, d, J=8.7 Hz), 7.4–7.6 (5H, m), 8.0–8.2 (3H, m), 8.33 (2H, d, J=8.4 Hz) APCI-MASS: m/z=468 $(M+H^+)$

Preparation 211

1-[5-[4-(4-n-Butoxyphenyl)phenyl]furan-2-yl-carbonyl] benzotriazole 3-oxide

IR (KBr): 2958, 2871, 1781, 1678, 1603, 1535, 1479, 1265 cm^{-1} NMR ($CDCl_3$, δ): 1.00 (3H, t, J=7.3 Hz), 1.4–1.9 (4H, m), 4.02 (2H, t, J=6.4 Hz), 6.9–7.1 (3H, m), 7.4–8.2 (11H, m) APCI-MASS: m/z=351 (Methyl ester)

Preparation 212

1-(3-(S)-Hydroxy-2-benzylhexadecanoyl)benzotriazole 3-oxide

IR (Neat: 2854.1, 1814.7, 1459.8,, 742.5 cm^{-1}

Preparation 213

1-(3-(R)-Benzyloxycarboxylamino-18-methoxyoctadecanoyl)benzotriazole 3-oxide

IR (KBr): 1805.0, 1729.8, 1695.1 cm^{-1} NMR (DMSO-d_6, δ): 1.1–1.65 (30H, m), 3.20 (3H, s), 3.28 (2H, t, J=6.5 Hz), 4.01 (1H, m), 5.06 (2H, s), 7.32 (5H, m), 7.4–7.8 (3H, m), 8.12 (1H, d, J=7 Hz)

Preparation 214

1(3-(S)-Hydroxyhexadecanoyl)benzotriazole 3-oxide

IR (KBr): 1710.6, 1498.4, 1429.0, 771.4 cm^{-1} NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.4 Hz), 1.2–1.7 (24H, m), 2.00 (1H, s), 3.1–3.5 (2H, m), 4.30 (1H, m), 7.59 (1H, t, J=7 .8 Hz), 7.81 (1H, t, J=7.8 Hz), 8.02 (1H, d, J=8.3 Hz), 8.42 (1H, d, J=8.3 Hz)

Preparation 215

1-(3-Methyl-2-tridecenoyl)benzotriazole 3-oxide

IR (KBr): 2927.4, 1791.5, 1633.4, 1081.9 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.3 Hz), 1.1–1.7 (20H, m, 2.25 (3H, s), 6.08 (1H, s), 7.3–7.6 (3H, m), 8.06 (1H, d, J=8.2 Hz)

Preparation 216

1-[4-[4-[4-(8-Methyloxyoctyloxy)phenyl]piperazin-1-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 1780.0, 1600.6, 1511.9, 1234.2, 1184.1 cm^{-1} NMR ($CDCl_3$, δ): 1.3–1.9 (12H, m), 3.24 (4H, t, J=5.0 Hz), 3.33 (3H, s), 3.37 (2H, t, J=6.8 Hz), 3.62 (4H, t, J=5.0 Hz), 3.92 (2H, t, J=6.5 Hz), 6.8–7.1 (6H, m), 7.35–7.65 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.0 Hz)

Preparation 217

1-[3-Fluoro-4-[4-(4-n-hexyloxyphenyl)piperazine-1-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 1778.0 cm^{-}

Preparation 218

1-[3-Chloro-4-[4-(4-n-hexyloxyphenyl)piperazin-1-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 1778.0, 1594.8, 1511.9, 1218.8 cm^{-1} NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.5 Hz), 1.2–1.6 (6H, m), 1.6–1.9 (2H, m), 3.29 (4H, t, J=3.6 Hz), 3.44 (4H, t, J=3.6 Hz), 3.93 (2H, t, J=6.5 Hz), 6.87 (2H, d, J=9.2 Hz), 6.97 (2H, d, J=9.2 Hz), 7.19 (1H, d, J=8.6 Hz), 7.4–7.7 (3H, m), 8.10 (1H, d, J=6.4 Hz), 8.14 (1H, dd, J=8.6 and 2.1 Hz), 8.27 (1H, d, J=2.1 Hz) APCI-MASS: m/z=534 (M^++H)

Preparation 219

1-[4-(4-Piperidinopiperidin-1-yl)benzoyl]benzotriazole 3-oxide

IR (KBr): 1758.8, 1602.6, 1186.0 cm^{-1} NMR ($CDCl_3$, δ): 1.35–1.8 (8H, m), 1.96 (2H, d, J=13 Hz), 2.45–2.7 (5H, m), 2.97 (2H, td, J=12.8 and 2.6 Hz), 4.04 (2H, d, J=13 Hz), 6.93 (2H, d, J=9.2 Hz), 7.35–7.6 (3H, m), 8.1–8.4 (3H, m)

Preparation 220

1-[3-[4-(4-n-Hexyloxyphenyl)piperazin-1yl]pyridazin-6-yl-carbonyl]benzotriazole 3-oxide

IR (KBr): 1787.7, 1585.2, 1511.9, 1240.0 cm^{-1}

Preparation 221

1-[5-[4-(4-n-Hexyloxyphenyl)piperazin-1-yl]picolinoyl] benzotriazole 3-oxide

IR (KBr): 1766.5, 1575.6, 1511.9, 1232.3 cm^{-1} NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.5 Hz), 1.2–1.6 (6H, m), 1.65–1.9 (2H, m), 3.27 (4H, t, J=5.1 Hz), 3.66 (4H, t, J=5.1 Hz), 3.93 (2H, t, J=6.5 Hz), 6.88 (2H, d, J=9.2 Hz), 6.95 (2H, d, J=9.2 Hz), 7.25 (1H, dd, J=7.6 and 2.9 Hz), 7.35–7.6 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.18 (1H, d, J=8.9 Hz), 8.52 (1H, d, J=2.9 Hz) APCI-MASS: m/z=501 (M^++H)

Preparation 222

1-[4-[4-(4-Cyclohexylphenyl)piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1770.3, 1602.6, 1515.8, 1232.3, 1186.0 cm^{-1} NMR ($CDCl_3$, δ): 1.15–1.5 (6H, m), 1.65–2.0 (4H, m), 2.45 (1H, m), 3.33 (4H, t, J=5.1 Hz), 3.62 (4H, t, J=5.1 Hz), 6.92 (2H, d, =8.7 Hz), 6.99 (2H, d, J=9.2 Hz), 7.16 (2H, d, J=8.7 Hz), 7.35–7.65 (3H, m), 8.09 (1H, d, J=8.21 Hz), 8.15 (2H, d, J=9.2 Hz)

Preparation 223

1-[4-[4-(4-n-Hexylphenyl)piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1768.4, 1602.6, 1515.8, 1230.4, 1184.1 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.5 Hz), 1.2–1.45 (6H, m), 1.5–1.7 (2H, m), 2.55 (2H, t, J=7.6 Hz), 3.2–3.4 (4H, m), 3.5–3.7 (4H, m), 6.91 (2H, d, J=8.6 Hz), 7.00 (2H, d, J=9.1 Hz), 7.13 (2H, d, J=8.5 Hz), 7.35–7.6 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.1 Hz)

Preparation 224

1-[4-[4-(4-Phenylcyclohexyl)piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1780.0, 1762.6, 1602.6, 1234.2, 1182.2 cm^{-1} NMR ($CDCl_3$, δ): 1.3–1.7 (4H, m), 1.95–2.15 (4H, m), 2.35–2.6 (2H, m), 2.79 (4H, t, J=5.0 Hz), 3.49 (4H, t, J=5.0 Hz), 6.95 (2H, d, J=9.0 Hz), 7.1–7.35 (5H, m), 7.35–7.6 (3H, m), 8.08 (1H, d, J=7.1 Hz), 8.12 (2H, d, J=9.0 Hz)

Preparation 225

1-[4-[4-[1-(4-n-Hexyloxyphenyl)piperidin-4-yl]piperazin-1-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1768.4, 1602.6, 1511.9, 1234.2 cm^{-1} NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.55 (6H, m), 1.6–1.9 (4H, m), 1.96 (2H, d, J=11 Hz), 2.44 (1H, m), 2.64 (2H, d, J=1.1 Hz), 2.77 (4H, t, J=5.0 Hz), 3.48 (4H, t, J=5.0 Hz), 3.59 (2H, d, J=11 Hz), 3.91 (2H, t, J=6.5 Hz), 6.7–7.05 (6H, m), 7.35–7.6 (3H, m), 8.08 (1H, d, J=6.9 Hz), 8.12 (2H, d, J=7.7 Hz)

Preparation 226

1-[4-(4-Trans-n-pentylcylcohexyl)benzoyl]benzotriazole 3-oxide

IR (KBr): 1799.3, 1778.0, 1608.3, 1228.4, 977.7 cm^{-1} NMR ($CDCl_3$,δ): 0.91 (3H, t, J=6.6 Hz), 1.0–1.7 (13H, m), 1.93 (4H, d, J=9.8 Hz), 2.62 (1H, t, J=12 Hz), 7.35–7.6 (5H, m), 8.09 (1H, d, J=7.9 Hz), 8.19 (2H, d, J=8.4 Hz)

Preparation 227

1-[6-(8-Methoxyoctyloxy)-2-naphthoyl]benzotriazole 3-oxide

IR (KBr): 2931.3, 2856.1, 1778.0, 1623.8 cm^{-1}

Preparation 228

1-(E)-[3-[4-[4-(7-Fluoroheptyloxy)phenyl]phenyl]acryloyl] benzotriazole 3-oxide

IR (KBr): 3070.1, 2935.1, 2859.9, 1700.9, 1619.9, 1596.8 cm^{-1} NMR ($CDCl_3$, δ): 1.30–2.00 (10H, m), 4.02 (2H, t, J=6.4 Hz), 4.45 (2H, dt, J=47.5 and 6.2 Hz), 6.70–8.65 (14H, m)

Preparation 229

1-(6-Heptylnaphthalene-2-carbonyl)benzotriazole 3-oxide

NMR (DMSO-d_6, δ): 0.75–0.93 (3H, m), 1.10–1.45 (8H, m), 1.55–1.80 (2H, m), 2.68–2.90 (2H, m), 7.35–9.06 (10H, m) APCI-MASS: m/z=388 (M^++1)

Preparation 230

1-(E)-[3-[4-[4-(8-Methoxyoctyloxy)phenyl]phenyl] acryloyl]benzotriazole 3-oxide

Preparation 231

1-(E)-[3-[4-[4-(5-Hexenyloxy)phenyl]phenyl]acryloyl] benzotriazole 3-oxide

IR (KBr): 3072.0, 3033.5, 2939.0, 2865.7, 1780.0, 1693.2, 1619.9, 1596.8 cm^{-1} NMR (DMSO-d_6, δ): 1.43–1.66 (2H, m), 1.66–1.90 (2H, m), 2.02–2.23 (2H, m), 3.90–4.16 (2H, m), 4.90–5.13 (2H, m), 5.72–6.00 (1H, m), 6.93–8.30 (14H, m) APCI-MASS: m/z=337 (Methyl ester, M^++1)

Preparation 232

1-(E)-[3-[4-[4-(4-Methylpentyloxy)phenyl]phenyl] acryloyl]benzotriazole 3-oxide

IR (KBr): 3072.0, 3033.5, 2952.5, 2869.6, 1780.0, 1693.2, 1618.0, 1598.7 cm^{-1} NMR (DMSO-d_6, δ); 0.90 (6H, d, J=6.5 Hz), 1.20–1.40 (2H, m), 1.50–1.90 (3H, m), 3.90–4.10 (2H, m), 6.40–8.30 (14H, m) APCI-MASS: m/z=442 (M^++1)

Preparation 233

1-(E)-[3-[4-[4-(6-Fluorohexyloxy)phenyl]phenyl]acryloyl] benzotriazole 3-oxide

IR (KBr): 3074.0, 3033.5, 2939.0, 2865.7, 1780.0, 1697.1, 1598.7 cm^{-1} NMR (DMSO-d_6, δ): 1.25–1.83 (6H, m), 4.04 (2H, t, J=6.5 Hz), 4.45 (2H, dt, J=47.5 and 6.5 Hz), 6.9–8.3 (14H, m) APCI-MASS: m/z=460 (M^++1)

Preparation 234

1-(E)-[3-[4-[4-(6-Methoxyhexyloxy)phenyl]phenyl] acryloyl]benzotriazole 3-oxide

NMR (DMSO-d_6, δ): 1.30–1.65 (6H, m), 1.65–1.90 (2H, m), 3.22 (3H, s), 3.22–3.40 (2H, m), 4.02 (2H, t, J=6.5 Hz), 6.5–8.3 (14H, m)

Preparation 235

1-[4-[3-(4-n-Hexyloxyphenyl)pyrazol-5-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2935, 1780, 1610, 1506, 1249, 1232, 1178, 1087 cm^{-1} NMR ($CDCl_3$, δ): 0.91 (3H, d, J=6.4 Hz), 1.2–1.6 (6H, m), 1.7–1.9 (2H, m), 3.98 (2H, t, J=6.5 Hz), 6.8–7.0 (3H, m), 7.4–7.6 (5H, m), 8.00 (2H, d, J=8.4 Hz), 8.10 (1H, d, J=8.1 Hz), 8.28 (1H, d, J=8.4 Hz) APCI-MASS: m/z=482 ($M+H^+$)

Preparation 236

1-[4-[4-[4-(6-Methoxyhexyloxy)phenyl]phenyl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2935, 2858, 1774, 1600, 1490, 1257, 1211 cm^{-1} NMR ($CDCl_3$, δ): 1.4–1.9 (8H, m), 3.35 (3H, s), 3.40 (2H, t, J=6.3 Hz), 4.02 (21H, t, J=6.4 Hz), 7.00 (2H, d, J=8.7 Hz), 7.4–7.8 (7H, m), 7.87 (2H, d, J=8.4 Hz), 8.12 (1H, d, J=8.2 Hz), 8.36 (2H, d, J=8.4 Hz) APCI-MASS: m/z=522 ($M+H^+$)

Preparation 237

1-[4-[5-[4-(8-Methoxyoctyloxy)phenyl]-1,3,4-thiadiazol-2-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 2929, 2854, 1776, 1602, 1469, 1255 cm^{-1} NMR ($CDCl_3$, δ): 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.33 (3H, s), 3.37 (2H, d, J=6.4 Hz), 4.03 (2H, d, J=6.5 Hz), 7.00 (2H, d, J=8.9 Hz), 7.4–7.6 (3H, m), 7.97 (2H, d, J=8.9 Hz), 8.12 (1H, d, J=8.2 Hz), 8.23 (2H, d, J=8.7 Hz), 8.39 (2H, d, J=8.7 Hz) APCI-MASS: m/z=558 ($M+H^+$)

Preparation 238

1-[4-(4-n-Butoxyphenyl)cinnamoyl]benzotriazole 3-oxide

IR (KBr): 2952, 2867, 1778, 1598, 1496, 1249, 1186 cm^{-1} NMR ($CDCl_3$, δ): 0.99 (3H, t, J=7.3 Hz), 1.55 (2H, tq, J=7.0 and 7.3 Hz), 1.78 (2H, tt, J=7.0 and 6.4 Hz), 4.02 (2H, t, J=6.4 Hz), 6.75 (1H, d, J=16.0 Hz), 7.00 (2H, d, J=8.7 Hz), 7.4–8.2 (9H, m) APCI-MASS: m/z=414 ($M+H^+$)

Preparation 239

1-[4-[5-(4-Cyclohexylphenyl)-1,3,4-thiadiazol-2-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2925, 2850, 1778, 1230, 989 cm^{-1} NMR ($CDCl_3$, δ): 1.2–1.6 (5H, m), 1.7–2.0 (5H, m), 2.5–2.7 (1H, m), 7.37 (2H, d, J=8.3 Hz), 7.4–7.6 (3H, m), 7.97 (2H, d, J=8.3 Hz), 8.13 (1H, d, J=8.2 Hz), 8.26 (2H, d, J=8.6 Hz), 8.42 (2H, d, J=8.6 Hz) APCI-MASS: m/z=482 $(M+H)^+$

Preparation 240

1-[4-[5-[4-(4-n-Propyloxyphenyl)phenyl]-1,3,4-oxadiazol-2-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1778, 1604, 1488, 1249, 1232, 998 cm^{-1} NMR ($CDCl_3$, δ): 1.07 (3H, t, J=7.4 Hz), 1.85 (2H, tq, J=6.5 and 7.4 Hz), 7.02 (2H, d, J=8.8 Hz), 7.4–7.7 (3H, m), 7.61 (2H, d, J=8.8 Hz), 7.75 (2H, d, J=8.5 Hz), 8.14 (1H, d, J=8.2 Hz), 8.22 (2H, d, J=8.5 Hz), 8.40 (2H, d, J=8.8 Hz), 8.48 (2H, d, J=8.8 Hz) APCI-MASS: m/z=518 $(M+H)^+$

Preparation 241

1-[4-(5-n-Nonyl-1,3,4-oxadiazol-2-yl)benzoyl] benzotriazole 3-oxide

IR (KBr): 2919, 2850, 1780, 1565, 1415, 1251 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.6 (12H, m), 1.8–2.0 (2H, m), 2.98 (2H, t, J=7.7 Hz), 7.4–7.6 (3H, m), 8.12 (1H, d, J=9.0 Hz), 8.28 (2H, d, J=8.7 Hz), 8.42 (2H, d, J=8.7 Hz) APCI-MASS: m/z=434 ($M+H^+$)

Preparation 242

1-[4-[3-(4-n-Hexyloxyphenyl)-1,2,4-oxadiazol-5-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2946, 2869, 1780, 1251, 1230, 1001 cm^{-1} NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.8 Hz), 1.3–1.6 (6H, m), 1.8–1.9 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.03 (2H, d, J=8.9 Hz), 7.4–7.6 (3H, m), 8.0–8.2 (3H, m), 8.46 (4H, s) APCI-MASS: m/z=484 ($M+H^+$)

Preparation 243

1-[4-[5-(4-n-Octyloxyphenyl)-1,3,4-thiadiazol-2-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2925, 2856, 1774, 1602, 1259, 1232, 989 cm^{-1} NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.7 Hz), 1.1–1.6 (10H, m), 1.7–1.9 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.01 (2H, d, J=8.9 Hz), 7.4–7.6 (3H, m), 7.97 (2H, d, J=8.8 Hz), 8.12 (1H, d, J=8.2 Hz), 8.24 (2H, d, J=8.6 Hz), 8.40 (2H, d, J=8.6 Hz) APCI-MASS: m/z=528 ($M+H^+$)

Preparation 244

1-[4-[5-(4-Trans-n-pentylcyclohexyl)-1,3,4-thiadiazol-2-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2952, 2919, 2848, 1785, 1444, 1226, 991 cm^{-1} NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.9 Hz), 1.0–1.7 (13H, m), 1.94 (2H, d, J=12.0 Hz), 2.27 (2H, d, J=12.0 Hz), 3.19 (1H, tt, J=12.0 and 3.6 Hz), 7.4–7.6 (3H, m), 8.12 (1H, d, J=8.0 Hz), 8.19 (2H, d, J=8.6 Hz), 8.38 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=476 ($M+H^+$)

Preparation 245

1-[4-[3-(4-n-Pentyloxyphenyl)isoxazol-5-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2948, 2867, 1776, 1610, 1436, 1253, 1002 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=7.1 Hz), 1.2–1.6 (4H, m), 1.7–1.9 (2H, m), 4.02 (2H, t, J=6.5 Hz), 7.0–7.1 (3H, m), 7.4–7.6 (3H, m), 7.81 (2H, d, J=8.8 Hz), 8.06 (2H, d, J=8.6 Hz), 8.12 (1H, d, J=8.0 Hz), 8.39 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=469 ($M+H^+$)

Preparation 246

1-[4-[5-[4-(8-Methoxyoctyloxy)phenyl]-1,3,4-oxadiazol-2-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 2923, 2854, 1787, 1608, 1494, 1255, 1228, 993 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.34 (3H, s), 3.38 (2H, t, J=6.4 Hz), 4.05 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.8 Hz), 7.4–7.6 (3H, s), 8.1–8.2 (3H, s), 8.36 (2H, d, J=8.7 Hz), 8.45 (2H, d, J=8.7 Hz)

APCI-MASS: m/z=542 ($M+H^+$)

Preparation 247

1-[4-[4-(6-Phenylpyridazin-3-yl-oxy]phenyl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1783, 1604, 1423, 1284, 985 cm^{-1}

NMR ($CDCl_3$, δ): 7.2–8.2 (15H, m), 8.12 (2H, d, J=8.3 Hz), 8.36 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=486 (M^++1)

Preparation 248

1-[4-[5-(4-n-Octyloxyphenyl)-1,3,4-oxadiazol-2-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2925, 2854, 1780, 1610, 1496, 1257, 1228, 1180 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–2.0 (12H, m), 4.05 (2H, t, J=6.5 Hz), 7.05 (2H, d, J=8.7 Hz), 7.4–7.6 (3H, m), 8.0–8.2 (3H, m), 8.37 (2H, d, J=8.6 Hz), 8.45 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=512 ($M+H^+$)

Preparation 249

1-[4-[2-(4-n-Hexyloxyphenyl)pyrimidin-6-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2948, 2861, 1780, 1552, 1413, 1378, 987 cm^{-1}

NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.8 Hz), 1.2–1.6 (6H, m), 1.8–2.0 (2H, m), 4.06 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=9.0 Hz), 7.4–7.6 (3H, m), 7.64 (1H, d, J=5.2 Hz), 8.13 (1H, d, J=8.2 Hz), 8.44 (4H, s), 8.55 (2H, d, J=9.0 Hz), 8.90 (1H, d, J=5.2 Hz)

APCI-MASS: m/z=494 ($M+H^+$)

Preparation 250

1-[4-[4-[8-(2-Ethoxyethoxy)octyloxy]phenyl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2933, 2861, 1778, 1598, 1247, 1186, 977 cm^{-1}

NMR ($CDCl_3$, δ): 1.22 (3H, t, J=7.0 Hz), 1.3–2.0 (14H, m), 3.4–3.6 (6H, m), 4.02 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.8 Hz), 7.4–7.6 (3H, m), 7.62 (2H, d, J=8.8 Hz), 7.78 (2H, d, J=8.6 Hz), 8.10 (1H, d, J=8.9 Hz), 8.31 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=532 ($M+H^+$)

Preparation 251

1-[4-[4-[7-(Piperidin-1-yl-carbonyl)heptyloxy]phenyl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2935, 2856, 1774, 1631, 1598, 1255, 1191 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–2.0 (16H, m), 2.37 (2H, t, J=7.6 Hz), 3.48 (4H, s), 4.02 (2H, t, J=6.4 Hz), 7.02 (2H, d, J=8.6 Hz), 7.4–7.6 (3H, m), 7.63 (2H, d, J=8.6 Hz), 7.78 (2H, d, J=8.3 Hz), 8.11 (1H, d, J=8.1 Hz), 8.31 (2H, d, J=8.3 Hz)

APCI-MASS: m/z=541 ($M+H^+$)

Preparation 252

1-[6-[4-(4-n-Heptyloxyphenyl)piperazin-1-yl]nicotinoyl] benzotriazole 3-oxide

IR (KBr): 2929, 2856, 1762, 1604, 1510, 1240 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.9 (10H, m), 3.20 (4H, t, J=5.0 Hz), 3.8–4.0 (6H, m), 6.75 (1H, d, J=9.5 Hz), 6.86 (2H, d, J=9.3 Hz), 6.95 (2H, d, J=9.3 Hz), 7.3–7.6 (3H, m), 8.10 (1H, d, J=8.2 Hz), 8.19 (1H, dd, J=9.2 and 2.3 Hz), 9.05 (1H, d, J=2.3 Hz)

APCI-MASS: m/z=515 ($M+H^+$)

Preparation 253

1-[6-[4-[4-(8-Methoxyoctyloxy)phenyl]piperazin-1-yl] nicotinoyl]benzotriazole 3-oxide

IR (KBr): 2929, 2854, 1766, 1602, 1510, 1419, 1234 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.9 (12H, m), 3.2–3.3 (4H, m), 3.33 (3H, s), 3.36 (2H, t, J=6.4 Hz), 3.92 (2H, t, J=6.5 Hz), 4.0–4.2 (4H, m), 6.75 (1H, ,d, J=9.1 Hz), 6.87 (2H, d, J=8.9 Hz), 7.0–7.2 (2H, m), 7.4–7.6 (3H, m), 8.09 (1H, d, J=8.1 Hz), 8.20 (1H, dd, J=9.1 and 2.3 Hz), 9.05 (1H, d, J=2.3 Hz)

APCI-MASS: m/z=559 ($M+H^+$)

Preparation 254

1-[4-[5-[4-(4-n-Propyloxyphenyl)phenyl]-1,3,4-thiadiazol-2-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1774, 1600, 1234, 985 cm^{-1}

NMR ($CDCl_3$, δ): 1.07 (3H, t, J=7.3 Hz), 1.85 (2H, tq, J=6.5 and 7.3 Hz), 3.99 (2H, t, J=6.5 Hz), 7.01 (2H, d, J=8.7 Hz), 7.4–7.7 (5H, m), 7.72 (2H, d, J=8.7 Hz), 8.1–8.2 (2H, m), 8.28 (2H, d, J=8.6 Hz), 8.44 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=534 $(M+H)^+$

The following compounds (Preparation 255 to 256) were obtained according to a similar manner to that of Preparation 32.

Preparation 255

6-Heptylnaphthalene-2-carboxylic acid

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.15–1.53 (8H, m), 1.58–1.88 (2H, m), 2.80 (2H, t, J=7.6 Hz), 7.42 (1H, dd, J=1.7 and 8.4 Hz), 7.67 (1H, s), 7.84 (1H, d, J=8.6 Hz), 7.90 (1H, d, J=8.4 Hz), 8.09 (1H, dd, J=1.7 and 8.6 Hz), 8.68 (1H, s)

APCI-MASS: m/z=271 (M^++1), 285 (methyl $ester^+$−1)

Preparation 256

3-(E)-[4-[4-(7-Fluoroheptyloxy)phenyl]phenyl]acrylic acid

IR (KBr): 3037.3, 2935.1, 2861.8, 1679.7, 1633.4, 1600.6 cm^{-1}

NMR (DMSO-d_6, δ): 1.30–1.85 (10H, m), 4.01 (2H, t, J=6.4 Hz), 4.44 (2H, dt, J=47.6 and 6.1 Hz), 6.54 (1H, d, J=15.9 Hz), 7.02 (2H, d, J=8.7 Hz), 7.53–7.80 (7H, m)

Preparation 257

To a solution of 4-methylpentanol (3.0 ml) in pyridine (20 ml) were added in turn with p-toluenesulfonyl chloride (4.6 g) and 4-N,N-dimethylaminopyridine (1.5 g) at ambient temperature. After stirring at ambient temperature, the reaction mixture was taken up into a mixture of ethyl acetate (100 ml) and water (100 ml). The separated organic layer was washed in turn with hydrochloric acid(1N), water, aqueous sodium hydrogencarbonate, and brine, and dried over magnesium sulfate. Evaporation gave 1-p-Toluenesulfonyloxy-4-methylpentane (5.30 g).

NMR ($CDCl_3$, δ): 0.83 (6H, d, J=6.6 Hz), 1.48 (1H, sept, J=6.6 Hz), 1.50–1.70 (2H, m), 2.45 (3H, s), 4.00 (2H, t, J=6.6 Hz), 7.34 (2H, d, J=8.1 Hz), 7.79 (2H, d, J=8.1 Hz)

APCI-MASS: m/z=257 (M^++1)

Preparation 258

To a solution of 4-bromo-4'-n-butyloxybiphenyl (3.05 g) in tetrahydrofuran (60 ml) was added 1.55M n-butyllithium in n-hexane (7.74 ml) at −60° C. over a period of 10 minutes.

The solution was stirred at −30° C. for 1.5 hours and cooled to −60° C. To the solution was added triisopropylborate (3.46 ml) over a period of 5 minutes, and the mixture was stirred for 1.5 hours without cooling. To the solution was added 1N hydrochloric acid (20 ml) and the solution was stirred for 30 minutes and extracted with ethyl acetate. The organic layer was separated and washed with water, brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was triturated with n-hexane. The solid was collected by filtration and dried under reduced pressure to give 4-(4-n-Butyloxyphenyl)phenylboronic acid (2.31 g).

IR (KBr): 3398, 2956, 2919, 2871, 1604, 1531, 1392, 1257 cm^{-1}

NMR (DMSO-d_6, δ): 0.94 (3H, t, J=7.3 Hz), 1.4–1.8 (4H, m), 4.01 (2H, t, J=6.3 Hz), 7.01 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=7.9 Hz), 7.62 (2H, d, J=8.7 Hz), 7.84 (2H, d, J=7.9 Hz), 8.03 (2H, s)

The following compounds (Preparation 259 to 260) were obtained according to a similar manner to that of Preparation 258.

Preparation 259

4-[4-(6-Methoxyphexyloxy)phenyl]phenylboronic acid

IR (KBr): 3448, 3392, 2937, 2861, 1606, 1529, 1346, 1288 cm^{-1}

NMR (DMSO-d_6, δ): 1.3–1.8 (8H, m), 3.21 (3H, s), 3.31 (2H, t, J=6.3 Hz), 3.99 (2H, t, J=6.4 Hz), 7.00 (2H, d, J=8.7 Hz), 7.5–7.7 (4H, m), 7.84 (2H, d, J=8.1 Hz), 8.03 (2H, s)

APCI-MASS: m/z=329 $(M+H^+)$

Preparation 260

4-[4-(5-Methoxypentyloxy)phenyl]phenylboronic acid

IR (KBr): 3473, 3369, 3330, 2935, 2863, 1604, 1531, 1338, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 1.4–1.8 (6H, m), 3.22 (3H, s), 3.3–3.4 (2H, m), 3.99 (2H, ,t, J=6.4 Hz), 7.00 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.0 Hz), 7.61 (2H, d, J=8.7 Hz), 7.84 (2H, d, J=8.0 Hz), 8.04 (2H, s)

APCI-MASS: m/z=315 $(M+H^+)$

Preparation 261

To a suspension of 4-Methoxycarbonylphenyl boronic acid (648 mg) and 4-iodo-1-heptylpyrazole (876 mg) and $Pd(PPh_3)_4$ (173 mg) in 1,2-dimethoxyethane (10 ml) was added 2M Na_2CO_3 aq. (3.6 ml). The reaction mixture was stirred at 80° C. for 2 hours under N_2 atmosphere, and poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, and dried over $MgSO_4$. The solvent was removed under pressure. The residue was subjected to column-chromatography on silica gel 60 (Merk) and eluted with n-hexane/ethyl acetate (80:20). The fractions containing the object compound were combined and evaporated under reduced pressure to give 1-heptyl-4-(4-methoxycarbonylphenyl)pyrazole (0.20 g).

IR (KBr): 2952, 2920, 2848, 1712, 1610, 1288, 1114, 769 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 1.1–1.4 (8H, m), 1.7–1.9 (2H, m), 3.85 (3H, s), 4.11 (2H, t, J=7.0 Hz), 7.72 (2H, d, J=8.5 Hz), 7.93 (2H, d, J=8.5 Hz), 7.99 (1H, s), 8.34 (1H, s)

APCI-MASS: m/z=301 $(M+H^+)$

The following compounds (Preparations 262 to 268) were obtaining according to a similar manner to that of Preparation 261.

Preparation 262

Ethyl 4-[4-(4-n-butyloxyphenyl)phenyl]benzoate

IR (KBr): 2958, 2935, 2871, 1714, 1602, 1396, 1280, 1108 cm^{-1}

NMR ($CDCl_3$, δ): 0.99 (3H, t, J=7.3 Hz), 1.4–2.0 (7H, m), 4.02 (2H, t, J=6.4 Hz), 4.40 (2H, q, J=7.1 Hz), 6.98 (2H, d, J=6.8 Hz), 7.56 (2H, d, J=6.8 Hz), 7.66 (4H, s), 7.68 (2H, d, J=8.4 Hz), 8.12 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=375 $(M+H)^+$

Preparation 263

Methyl 6-(4-heptyloxyphenyl)nicotinate

IR (KBr): 2954, 2859, 1724, 1597, 1288, 1251, 1116, 783 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.6 Hz), 1.2–1.5 (8H, m), 1.7–1.9 (2H, m), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 7.00 (2H, d, J=8.8 Hz), 7.75 (1H, d, J=8.4 Hz), 8.02 (1H, d, J=8.8 Hz), 8.30 (1H, dd, J=8.4 and 2.2 Hz), 9.23 (1H, d, J=2.2 Hz)

APCI-MASS: m/z=328 $(M+H^+)$

Preparation 265

Methyl 5-[4-(4-n-butyloxyphenyl)phenyl]furan 2-carboxylate

IR (KBr): 2958, 2933, 2873, 1716, 1483, 1303, 1139 cm^{-1}

NMR ($CDCl_3$, δ): 0.99 (3H, t, J=7.3 Hz), 1.5–1.9 (4H, m), 3.93 (3H, s), 4.01 (2H, t, J=6.4 Hz), 6.75 (1H, d, J=3.6 Hz), 6.98 (2H, d, J=8.7 Hz), 7.26 (1H, d, J=3.6 Hz), 7.56 (2H, d, J=8.4 Hz), 7.61 (2H, d, J=8.7 Hz), 7.83 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=351 $(M+H)^+$ (2H, t, J=6.4 Hz), 4.01 (2H, t, J=6.4 Hz), 4.41 (2H, q, J=7.1 Hz), 6.98 (2H, d, J=8.7 Hz), 7.56 (2H, d, J=8.7 Hz), 7.6–7.8 (6H, m), 8.12 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=433 $(M+H^+)$

Preparation 267

4-[4-[4-(5-Methoxypentyloxy)phenyl]phenyl]benzoic acid

IR (KBr): 2939, 2859, 1679, 1587, 1396, 1321, 1292, 1126 cm^{-1}

NMR (DMSO-d_6, δ): 1.3–1.8 (6H, m), 3.21 (3H, s), 3.2–3.4 (2H, m), 4.01 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.6 Hz), 7.66 (2H, d, J=8.6 Hz), 7.7–7.9 (6H, m), 8.03 (2H, d, J=8.2 Hz)

APCI-MASS: m/z=391 $(M+H^+)$

Preparation 268

Methyl 4-[4-[4-(5-methoxypentyloxy)phenyl]phenyl] phenyl acetate

IR (KBr): 2937, 2863, 1739, 1604, 1492, 1255 cm^{-1}

NMR ($CDCl_3$, δ): 1.5–2.0 (6H, m), 3.34 (3H, s), 3.42 (2H, t, J=6.3 Hz), 3.68 (2H, s), 3.72 (3H, s), 4.02 (2H, t, J=6.4 Hz), 6.97 (2H, d, J=8.7 Hz), 7.36 (2H, d, J=8.2 Hz), 7.5–7.7 (8H, m)

APCI-MASS: m/z=419 $(M+H^+)$

Preparation 269

A solution of 3-[2-(4-Hexylphenylamino)ethyl]-2-oxo-oxazolidine hydrochloride (2.131 g) in 25% hydrobromic acid in acetic acid (13.04 ml) was stirred for 96 hours at ambient temperature. The reaction mixture was pulverized with diisopropyl ether. The precipitate was collected by

filtration and added to ethanol (15 ml). The solution was refluxed for 5 hours and pulverized with diisopropyl ether. The precipitate was collected by filtration to give 1-(4-n-Hexylphenyl)piperazine dihydrobromide (2.413 g).

IR (KBr): 2921.6, 2711.4, 2485.5, 1452.1, 1012.4 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.6 Hz), 1.1–1.4 (6H, m), 1.4–1.6 (2H, m), 2.49 (2H, t, J=8.4 Hz), 3.1–3.4 (8H, m), 6.54 (2H, s), 6.90 (2H, d, J=8.7 Hz), 7.08 (2H, d, J=8.7 Hz), 8.78 (1H, s)

APCI-MASS: m/z=247 (M^++H)

The following compounds (Preparations 270 to 274) were obtained according to a similar manner to that of Preparation 269.

Preparation 270

4-[4-(4-n-Hexylphenyl)piperazin-1-yl]benzoic acid dihydrobromide

IR (KBr): 2956.3, 1691.3, 1664.3, 1602.6, 1232.3 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.5 Hz), 1.2–1.4 (10H, m), 1.4–1.6 (2H, m), 2.51 (2H, t, J=7.4 Hz), 3.2–3.6 (8H, m), 7.0–7.2 (6H, m), 7.81 (2H, d, J=8.8 Hz)

APCI-MASS: m/z=367 (M^++H)

Preparation 271

1-[4-Cyclohexylphenyl)piperazine dihydrobromide

IR (KBr): 2927.4, 1510.0, 1452.1 cm^{-1}

NMR (DMSO-d_6, δ): 1.1–1.5 (6H, m), 1.6–1.9 (4H, m), 2.41 (1H, m), 3.1–3.4 (8H, m), 6.91 (2H, d, J=8.7 Hz), 7.11 (2H, d, J=8.7 Hz), 8.78 (1H, s)

APCI-MASS: m/z=245 (M^++H)

Preparation 272

4-[4-(4-Cyclohexylphenyl)piperazin-1-yl]benzoic acid dihydrobromide

IR (KBr): 1668.1, 1602.6, 1230.4, 1189.9 cm^{-1}

APCI-MASS: m/z=365 (M^++H)

Preparation 273

3-Fluoro-4-[4-(4-hydroxyphenyl)piperazin-1-yl]benzoic acid dihydrobromide

IR (KBr): 1708.6, 1610.3 cm^{-1}

NMR (DMSO-d_6, δ): 3.2–3.6 (8H, m), 6.81 (2H, d, J=8.6 Hz), 7.0–7.4 (3H, m), 7.4–7.8 (2H, m)

APCI-MASS: m/z=317 (M^++H)

Preparation 274

4-[4-(4-Hydroxyphenylpiperazin-1-yl]benzoic acid dihydrobromide

IR (KBr): 1670.1, 1604.5, 1226.5, 775.2 cm^{-1}

NMR (DMSO-d_6, δ): 3.0–3.2 (4H, m), 3.3–3.5 (4H, m), 6.68 (2H, d, J=8.8 Hz), 6.85 (2H, d, J=8.8 Hz), 7.02 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.8 Hz), 8.86 (1H, s), 12.29 (1H, s)

APCI-MASS: m/z=299 (M+H^+)

Preparation 275

A mixture of 4-n-hexyloxyaniline (10 g), ethyl acrylate (56.1 ml), glacial acetic acid (19.25 ml), and cuprous chloride (1.02 g) was heated under reflux with stirring under nitrogen for 26 hours. A solution of the cold product in ether was shaken with water and then with aqueous ammonia. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel and eluted with hexane-ethyl acetate (9:1). The fractions containing the object compound were combined and evaporated under reduced pressure to give Ethyl 3-[N-(2-ethoxycarbonylethyl)-N-(4-hexyloxyphenyl)amino] propionate (15.756 g).

IR (Neat): 1733.7, 1513.8, 1241.9, 1182.2 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.55 (6H, m), 1.24 (6H, t, J=7.1 Hz), 1.65–1.85 (2H, m), 2.51 (4H, t, J=7.2 Hz), 3.53 (4H, t, J=7.2 Hz), 3.89 (2H, t, J=6.5 Hz), 4.12 (4H, q, J=7.1 Hz), 6.72 (2H, d, J=9.3 Hz), 6.83 (2H, d, J=9.3 Hz)

APCI-MASS: m/z=394 (M^++H)

Preparation 276

A suspension of methyl 4-formylbenzoate (4.92 g) hydroxylamine hydrochloride (5.21 g) and sodium acetate (6.15 g) in ethanol (50 ml) was refluxed for 2 hours. The mixture was poured into water and extracted with ethyl acetate and the separated organic layer was washed with brine and dried over magnesium sulfate. The solvents were removed under reduced pressure to give 4-methoxycarbonylbenzaldehyde oxime (5.28 g).

IR (KBr): 3291, 1727, 1438, 1284, 1112 cm^{-1}

NMR ($CDCl_3$, δ): 3.93 (3H, s), 7.65 (2H, d, J=8.3 Hz), 8.10 (2H, d, J=8.3 Hz), 8.18 (1H, s), 8.27 (1H, s)

APCI-MASS: m/z=180

The following compound was obtained according to a similar manner to that of Preparation 276.

Preparation 277

N-Hydroxy-4-n-hexyloxybenzamidine

IR (KBr): 3446, 3349, 2937, 2865, 1650, 1610, 1519, 1392, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.4 Hz), 1.2–1.8 (8H, m), 3.97 (2H, t, J=6.5 Hz), 5.70 (2H, s), 6.90 (2H, d, J=8.4 Hz), 7.58 (2H, d, J=8.4 Hz), 9.43 (1H, s)

APCI-MASS: m/z=237 $(M+H)^+$

Preparation 278

To a solution of 4-methoxycarbonylbenzaldehyde oxime (896 mg) in N,N-dimethylformamide (10 ml) was added 4N-hydrochloride acid in 1,4-dioxane (1.38 ml) and oxone® (1.69 g). The suspension was stirred at ambient temperature for 16 hours and poured into ice-water. The object compound was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate. The solvents were removed under reduced pressure to give 4-Methoxycarbonylbenzaldehyde oxime chloride (1.05 g).

IR (KBr): 3390, 1710, 1436, 1405, 1284, 1232, 1116, 1016 cm^{-1}

NMR ($CDCl_3$, δ): 3.95 (3H, s), 8.93 (2H, d, J=8.3 Hz), 8.10 (2H, d, J=8.7 Hz), 8.39 (1H, s)

APCI-MASS: m/z=176 ($M-H^+$-HCl)

Preparation 279

A solution of Ethyl 4-oxo-1-(4-n-hexyloxyphenyl) piperidine-3-carboxylate (1.437 g) in 20% hydrochloric acid (7.2 ml) was refluxed for 2 hours, cooled, basified with 60% aqueous sodium hydroxide, and extracted with ethyl acetate.

The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure to give 1-(4-n-Hexyloxyphenyl)-4-piperidone (0.959 g).

IR (Neat): 2931.3, 1716.3, 1511.9, 1243.9, 825.4 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.6 (6H, m), 1.65–1.85 (2H, m), 2.57 (4H, t, J=6.1 Hz), 3.46 (4H, t, J=6.1 Hz), 3.92 (2H, t, J=6.5 Hz), 6.85 (2H, d, J=9.3 Hz), 6.95 (2H, d, J=9.3 Hz)

APCI-MASS: m/z=276 (M^++H)

Preparation 280

A solution of 4-[4-(7-Bromoheptyloxy)phenyl] bromobenzene (0.25 g) in a solution of tetra n-butylammonium fluoride (tetrahydrofuran solution, 1M 2.9 ml) was heated to 50° C. for 2 hours. After cooling to ambient temperature, the solution was taken up into a mixture of ethyl acetate (20 ml) and water (20 ml). The separated organic layer was washed with water, brine, and dried over magnesium sulfate. Evaporation gave a residue which was chromatographed on silica gel (30 ml) eluting with a mixture of n-hexane and ethyl acetate (100:0–97:3, V/V). The fractions which contained the objective compound were collected and evaporated a residue which was triturated with n-hexane to give 4-[4-(7-Fluoroheptyloxy) phenyl]bromobenzene (104 mg).

IR (KBr): 2937.1, 2859.9, 1606.4 cm^{-1}

NMR ($CDCl_3$, δ): 1.20–1.90 (10H, m), 3.99 (2H, t, J=6.4 Hz), 4.45 (2H, dt, J=47.3 and 6.1 Hz), 6.95 (2H, d, J=6.7 Hz), 7.40 (2H, d, J=6.7 Hz), 7.47 (2H, d, J=6.7 Hz), 7.52 (2H, d, J=6.7 Hz)

The following compound was obtained according to a similar manner to that of Preparation 280.

Preparation 281

4-[4-(6-Fluorohexyloxy)phenyl]bromobenzene

NMR ($CDCl_3$, δ): 1.40–1.95 (8H, m), 4.01 (2H, t, J=6.4 Hz), 4.47 (2H, dt, J=47.5 and 6.0 Hz), 6.95 (2H, d, J=8.6 Hz), 7.35–7.59 (6H, m)

Preparation 282

A solution of 4-[4-(8-Bromooctyloxy)phenyl] bromobenzene (3.7 g) in a mixture of sodium methoxide (4.9M in methanol, 17 ml), N,N-dimethylformamide (20 ml) and tetrahydrofuran (8 ml) was heated to 80° C. for 3 hours. The reaction mixture was taken up into a mixture of ethyl acetate (200 ml) and water (100 ml). The separated organic layer was washed in turn with water, brine, dried over magnesium sulfate. Evaporation gave a residue which was subjected to column chromatography (silica gel, 100 ml) eluting with n-hexane to give 4-[4-(8-Methoxyoctyloxy) phenyl]bromobenzene (2.73 g).

IR (KBr): 2935.1, 2858.0, 1604.5 cm^{-1}

NMR ($CDCl_3$, δ): 1.25–1.70 (10H, m), 1.70–1.95 (2H, m), 3.33 (3H, s), 3.37 (2H, t, J=6.5 Hz), 3.99 (2H, t, J=6.5 Hz), 6.95 (2H, d, J=8.8 Hz), 7.35–7.66 (6H, m)

APCI-MASS: m/z=391 (M^+)

The following compounds (Preparations 283 to 284) were obtained according to a similar manner to that of Preparation 282.

Preparation 283

4-[4-(6-Methoxyhexyloxy)phenyl]bromobenzene

NMR ($CDCl_3$, δ): 1.50–1.70 (6H, m), 1.70–1.95 (2H, m), 3.34 (3H, s), 3.40 (2H, t, J=6.2 Hz), 3.99 (2H, t, J=6.5 Hz), 6.95 (2H, d, J=8.7 Hz), 7.30–7.60 (6H, m)

APCI-MASS: m/z=365 (M^++2)

Preparation 284

4-[4-(7-Methoxyheptyloxy)phenyl]bromobenzene

IR (KBr): 2935.1, 2854.1, 1604.5 cm^{-1}

NMR ($CDCl_3$, δ): 1.25–1.70 (8H, m), 1.70–1.95 (2H, m), 3.33 (3H, s), 3.37 (2H, t, J=6.4 Hz), 3.98 (2H, t, J=6.5 Hz), 6.95 (2H, d, J=8.8 Hz), 7.35–7.56 (6H, m)

APCI-MASS: m/z=379 (M^++2)

Preparation 285

N-(4-octylphenyl)-N'-aminourea, Formamidine acetate (12.76 g) and N-carbazoyl-4-octylaniline (6.458 g) in N,N-dimethylformamide (19.4 ml) were stirred at 150° C. for 6 hours. The reaction mixture was pulverized with water. The precipitate was collected by filtration and washed with water to give 4-(4-Octylphenyl)-2,3-dihydro-4H-1,2,4-triazol-3-one (4.27 g).

IR (KBr): 3214.8, 3085.5, 1704.8 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.5–1.8 (2H, m), 2.64 (2H, t, J=7.9 Hz), 7.29 (2H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz), 7.67 (1H, d, J=1.3 Hz), 10.31 (1H, s)

APCI-MASS: m/z=274 ($M+H^+$)

The following compound (Preparation 286) was obtained according to a similar manner to that of Preparation 285.

Preparation 286

4-[4-(4-tert-Butoxycarbonylpiperazin-1-yl)phenyl]-2,3-dihydro-4H-1,2,4-triazol-3-one

IR (KBr): 3200, 1699.0, 918.0 cm^{-1}

NMR ($CDCl_3$, δ): 1.49 (9H, s), 3.17 (4H, t, J=4.9 Hz), 3.60 (4H, t, J=4.9 Hz), 7.00 (2H, d, J=9.0 Hz), 7.40 (2H, d, J=9.0 Hz), 7.63 (1H, s), 10.4 (1H, s)

APCI-MASS: m/z=346 ($M+H^+$)

Preparation 287

A mixture of Methyl 6-(1-heptynyl)naphthalene-2-carboxylate (4.51 g) and platinum oxide (0.4 g) in tetrahydrofuran was stirred under 3.5 atm pressure of hydrogen for 5 hours. The catalyst was filtered off and the filtlate was evaporated to give Methyl 6-heptylnaphthalene-2-carboxylate (4.40 g).

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.16–1.50 (8H, m), 1.50–1.80 (2H, m), 2.78 (2H, t, J=7.6 Hz), 3.97 (3H, s), 7.39 (1H, dd, J=17 and 8.4 Hz), 7.64 (1H, s), 7.79 (1H, d, J=8.6 Hz), 7.86 (1H, d, J=8.4 Hz), 8.02 (1H, dd, J=1.7 and 8.6 Hz), 8.57 (1H, s)

APCI-MASS: m/z=285 (M^++1)

The following compound (Preparation 288) was obtained according to a similar manner to that of Preparation 287.

Preparation 288

Methyl 6-hexylnaphthalene-2-carboxylate

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.8 Hz), 1.17–1.53 (6H, m), 1.60–1.82 (2H, m), 2.79 (2H, t, J=7.7 Hz), 3.97 (3H, s),

7.39 (1H, dd, J=1.7 and 8.4 Hz), 7.64 (1H, s), 7.80 (1H, d, J=8.6 Hz), 7.86 (1H, d, J=8.4 Hz), 8.03 (1H, dd, J=1.7 and 8.6 Hz), 8.57 (1H, s)

APCI-MASS: m/z=271 (M+1)

Preparation 289

To a stirred solution of Methyl 6-hydroxynaphthalene-2-carboxylate (3.0 g) in dichloromethane (40 ml) were added in turn diisopropylethylamine (3.9 ml) and triflic anhydride (3.0 ml) at −40° C. After stirring at −40° C. for 20 minutes, the mixture was taken up into a mixture of ethyl acetate and cold water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and dried in vacuo. The residue was taken up into piperidine (20 ml) and to the solution were added 1-heptyne (4.0 ml) and tetrakis (triphenylphosphine)palladium(0) (0.5 g). After heating to 85° C. for 1 hour under nitrogen atmosphere, the reaction mixture was evaporated in vacuo. The residue was diluted with ethyl acetate, and the solution was washed in turn with hydrochloric acid and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (9:1, V/V) to give Methyl 6-(1-heptynyl) naphthalene-2-carboxylate (4.01 g).

NMR ($CDCl_3$, δ): 0.94 (3H, t, J=7.1 Hz), 1.30–1.70 (6H, m), 2.46 (2H, t, J=7.0 Hz), 3.97 (3H, s), 7.50 (1H, dd, J=1.7 and 8.6 Hz), 7.80 (1H, d, J=8.6 Hz), 7.86 (1H, d, J=8.6 Hz), 8.04 (1H, dd, J=1.7 and 8.6 Hz), 8.55 (1H, s)

APCI-MASS: m/z=281 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 289.

Preparation 290

Methyl 6-(1-hexynyl)naphthalene-2-carboxylate

NMR ($CDCl_3$, δ): 0.97 (3H, t, J=7.1 Hz), 1.40–1.71 (4H, m), 2.47 (2H, t, J=6.8 Hz), 3.98 (3H, s), 7.50 (1H, dd, J=1.5 and 8.5 Hz), 7.79 (1H, d, J=8.6 Hz), 7.85 (1H, d, J=8.5 Hz), 7.92 (1H, s), 8.04 (1H, dd, J=1.7 and 8.6 Hz), 8.55 (1H, s)

APCI-MASS: m/z=267 (M^++1)

Preparation 291

To a solution of 4-octylaniline (5 ml) in a mixture of pyridine (12.5 ml) and chloroform (40 ml) was added phenyl chloroformate (2.95 ml) and stirred for 1.5 hours at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-Octyl-N-phenoxycarbonylaniline (4.51 g)

IR (KBr): 3318.9, 1714.4, 1234.2 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.2 Hz), 1.2–1.4 (10H, m), 1.5–1.7 (2H, m), 2.57 (2H, t, J=7.3 Hz), 6.88 (1H, s), 7.1–7.5 (9H, m)

The following compounds (Preparation 292 to 299) were obtained according to a similar manner to that of Preparation 291.

Preparation 292

4-(4-tert-Butoxycarbonylpiperazin-1-yl)-N-phenoxycarbonylaniline

IR (KBr): 3309.2, 1743.3, 1658.5, 1197.6 cm^{-1}

NMR ($CDCl_3$, δ): 1.48 (9H, s), 3.08 (4H, t, J=5.3 Hz), 3.58 (4H, t, J=5.3 Hz), 6.87 (1H, s), 6.91 (2H, d, J=9 Hz), 7.1–7.5 (7H, m)

APCI-MASS: m/z=398 ($M+H^+$)

Preparation 293

1-(4-Cyclohexylbenzoyl)-2-(4-methoxycarbonylbenzoyl)-hydrazine

IR (KBr): 3236, 2852, 1726, 1679, 1637, 1278, 1110 cm^{-1}

NMR (DMSO-d_6, δ): 1.1–1.5 (5H, m), 1.6–2.0 (5H, m), 2.60 (1H, m), 3.90 (3H, s), 7.37 (2H, d, J=8.0 Hz), 7.85 (2H, d, J=8.0 Hz), 8.0–8.2 (4H, m), 10.48 (1H, s), 10.68 (1H, s)

APCI-MASS: m/z=381 $(M+H)^+$

Preparation 294

1-[4-(Piperidin-1-yl)benzoyl]-2-(4-methoxycarbonylbenzoyl]hydrazine

IR (KBr): 3500, 3286, 2941, 2854, 1712, 1689, 1650, 1606, 1286, 1242 cm^{-1}

NMR (DMSO-d_6, δ): 1.59 (6H, s), 3.33 (4H, s), 3.90 (3H, s), 6.97 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.8 Hz), 8.02 (2H, d, J=8.4 Hz), 8.09 (2H, d, J=8.4 Hz), 10.23 (1H, s), 10.57 (1H, s)

APCI-MASS: m/z=382 $(M+H)^+$

Preparation 295

1-[4-(4-n-Propyloxyphenyl)benzoyl]-2-(4-methoxycarbonylbenzoyl]hydrazine

IR (KBr): 3230, 1724, 1679, 1654, 1280, 1108 cm^{-1}

NMR (DMSO-d_6, δ): 1.00 3H, d, J=7.5 Hz), 1.76 (2H, tq, J=6.5 and 7.5 Hz), 3.91 (3H, s), 7.05 (2H, d, J=8.7 Hz), 7.71 (2H, d, J=8.7 Hz), 7.79 (2H, d, J=8.5 Hz), 8.00 (2H, d, J=8.5 Hz), 8.05 (2H, d, J=8.6 Hz), 8.11 (2H, d, J=8.6 Hz), 10.60 (1H, s), 10.72 (1H, s)

APCI-MASS: m/z=433 $(M+H)^+$

Preparation 296

1-(4-Methoxycarbonylbenzoyl)-2-decanoylhydrazine

IR (KBr): 3220, 2919, 2850, 1724, 1643, 1600, 1567, 1479, 1284 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.7 (14H, m), 2.18 (2H, t, J=7.4 Hz), 3.89 (3H, s), 7.97 (2H, d, J=8.5 Hz), 8.06 (2H, d, J=8.5 Hz), 9.15 (1H, s), 10.49 (1H, s)

APCI-MASS: m/z=349 ($M+H^+$)

Preparation 297

1-(4-Methoxycarbonylbenzoyl)-2-(trans-4-n-pentylcyclohexylcarbonyl)hydrazine

IR (KBr): 3201, 2923, 2852, 1727, 1600, 1567, 1479, 1282 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.9 Hz), 0.9–1.0 (2H, m), 1.1–1.5 (11H, m), 1.7–1.9 (4H, m), 2.20 (1H, m), 3.88 (3H, s), 7.97 (2H, d, J=8.6 Hz), 8.06 (2H, d, J=8.6 Hz), 9.85 (1H, s), 10.46 (1H, s)

APCI-MASS: m/z=375 ($M+H^+$)

Preparation 298

1-[4-(8-Methoxyoctyloxy)benzoyl]-2-(4-methoxycarbonylbenzoyl)hydrazine

IR (KBr): 3213, 2935, 2856, 1718, 1600, 1567, 1465, 1282 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.8 (12H, m), 3.21 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.90 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.04

(2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz), 8.04 (2H, d, J=8.7 Hz), 8.10 (2H, d, J=8.7 Hz), 10.41 (1H, s), 10.64 (1H, s)

APCI-MASS: m/z=457 ($M+H^+$)

Preparation 299

1-(4-Octyloxybenzoyl)-2-(4-methoxycarbonylbenzoyl) hydrazine

IR (KBr): 3224, 2923, 2854, 1724, 1681, 1643, 1502, 1434, 1282, 1253, 1106 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 3.89 (3H, s), 4.04 (2H, t, J=6.3 Hz), 7.04 (2H, d, J=8.7 Hz), 7.90 (2H, d, J=8.7 Hz), 8.03 (2H, d, J=8.6 Hz), 8.10 (2H, d, J=8.6 Hz), 10.42 (1H, s), 10.64 (1H, s)

APCI-MASS: m/z=427 ($M+H^+$)

Preparation 300

A solution of Methyl 4-n-hexyloxybenzoate (2.00 g) and hydrazine hydrate (4.24 g) in ethanol (10 ml) was refluxed for 6 hours. After cooling, the reaction mixture was poured into water. The precipitate was collected by filtration, washed with water and dried over P_2O_5 under reduced pressure to give N-(4-n-hexyloxybenzoyl)hydrazine (1.96 g).

IR (KBr): 3311, 2954, 2869, 1623, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.8 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 4.00 (2H, t, J=6.5 Hz), 4.40 (2H, s), 6.95 (2H, d, J=8.6 Hz), 7.77 (2H, d, J=8.6 Hz), 9.59 (1H, s)

APCI-MASS: m/z=237 $(M+H)^+$

The following compounds (Preparation 301 to 308) were obtained according to a similar manner to that of Preparation 300.

Preparation 301

N-(4-Octylphenyl)-N'-aminourea

IR (KBr): 3309.2, 1683.6, 1554.3 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 1.1–1.4 (10H, m), 1.4–1.6 (2H, m), 2.48 (2H, t, J=8.9 Hz), 4.32 (2H, s), 7.03 (2H, d, J=8.4 Hz), 7.32 (1H, s), 7.38 (2H, d, J=8.4 Hz), 8.50 (1H, s)

Preparation 302

N-[4-(4-tert-Butoxycarbonylpiperazin-1-yl)phenyl]-N'-aminourea

IR (KBr): 3237.9, 1695.1, 1670.1, 1540.8, 1230.4 cm^{-1}

NMR (DMSO-d_6, δ): 1.42 (9H, s), 2.97 (4H, t, J=4.9 Hz), 3.44 (4H, t, J=4.9 Hz), 4.30 (2H, s), 6.85 (2H, d, J=9.0 Hz), 7.26 (1H, s), 7.36 (2H, d, J=9.0 Hz), 8.41 (1H, s)

Preparation 303

4-Cyclohexylbenzoylhydrazine

IR (KBr): 3318, 2925, 2852, 1625, 1606, 1527, 1326 cm^{-1}

NMR (DMSO-d_6, δ): 1.1–1.5 (5H, m), 1.6–2.0 (5H, m), 2.4–2.6 (1H, m), 4.44 (2H, s), 7.27 (2H, d, J=8.2 Hz), 7.73 (2H, d, J=8.2 Hz), 9.66 (1H, s)

APCI-MASS: m/z=219 $(M+H)^+$

Preparation 304

4-(Piperidin-1-yl)benzoylhydrazine

IR (KBr): 3263, 2852, 1612, 1504, 1245, 1124 cm^{-1}

NMR (DMSO-d_6, δ): 1.57 (6H, s), 3.25 (4H, s), 4.35 (2H, s), 6.90 (2H, d, J=9.0 Hz), 7.68 (2H, d, J=9.0 Hz), 9.44 (1H, s)

APCI-MASS: m/z=220 $(M+H)^+$

Preparation 305

4-(4-n-Propyloxyphenyl)benzoylhydrazine

IR (KBr): 3350, 3276, 1610, 1494, 1288, 978 cm^{-1}

NMR (DMSO-d_3, δ): 0.99 (3H, t, J=7.5 Hz), 1.75 (2H, tq, J=6.5 and 7.5 Hz), 3.98 (2H, t, J=6.5 Hz), 4.50 (2H, s), 7.03 (2H, d, J=8.8 Hz), 7.65 (2H, d, J=8.8 Hz), 7.69 (2H, d, J=8.4 Hz), 7.88 (2H, d, J=8.4 Hz), 9.79 (1H, s)

APCI-MASS: m/z=271 ($M+H^+$)

Preparation 306

4-Methoxycarbonylbenzoylhydrazine

IR (KBr): 3322, 3250, 3018, 1727, 1658, 1621, 1565, 1432, 1280, 1110 cm^{-1}

NMR (DMSO-d_6, δ): 3.87 (3H, s), 4.58 (2H, s), 7.93 (2H, dd, J=8.6 and 3.1 Hz), 7.02 (2H, dd, J=8.6 and 3.1 Hz), 9.97 (1H, s)

APCI-MASS: m/z=195 ($M+H^+$)

Preparation 307

Trans-4-n-pentylcyclohexylcarbonylhydrazine

IR (KBr): 3303, 3199, 2954, 2925, 2850, 1639, 1619, 1533, 1457 cm^{-1}

NMR (DMSO-d_6, δ): 0.8–1.0 (6H, m), 1.1–1.5 (10H, m), 1.6–2.2 (5H, m), 4.10 (2H, s), 8.85 (1H, s)

APCI-MASS: m/z=213 ($M+H^+$)

Preparation 308

4-(8-Methoxyoctyloxy)benzoylhydrazine

IR (KBr): 3309, 2937, 2852, 1606, 1494, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.8 (12H, m), 3.20 (3H, s), 3.25 (2H, t, J=6.5 Hz), 3.99 (2H, t, J=6.5 Hz), 4.39 (2H, s). 6.95 (2H, d, J=8.8 Hz), 7.7 (2H, d, J=8.8 Hz), 9.58 (1H, s)

APCI-MASS: m/z=295 $(M+H)^+$

Preparation 309

To a stirred solution of 4-bromo-4'-n-heptylbiphenyl (2.71 g) in tetrahydrofuran (100 ml) was added dropwise a solution of n-butyllithium in a mixture of diethyl ether and n-hexane (1.6M, 5.1 ml) at −78° C. After stirring at −78° C. for 30 minutes, the resultant mixture was added to a solution of diethyl oxalate (3.4 ml) in tetrahydrofuran (50 ml) at −78° C. The resultant mixture was allowed to warm to 0° C. for about 1 hour, and to the mixture was added acetic acid (0.5 ml). Evaporation gave a residue which was taken up into a mixture of water and ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate. Evaporation gave a residue which was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (10:0–95:5, V/V) to give 1-Ethyl-2-(4-n-heptylphenyl)ethanedione (2.23 g).

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.10–1.50 (8H, m), 1.44 (3H, t, J=7.1 Hz), 1.50–1.80 (2H, m), 2.66 (2H, t, J=7.7 Hz), 4.47 (2H, q, J=7.1 Hz), 7.20–7.40 (2H, m), 7.50–7.64 (2H, m), 7.64–7.85 (2H, m), 8.00–8.20 (2H, m)

APCI-MASS: m/z=353 (M^++1)

Preparation 310

To a suspension of sodium hydride (60% in oil, 0.37 g) in tetrahydrofuran (40 ml) was added by portions 4-acetyl-4'-n-heptylbiphenyl (2.50 g) at ambient temperature. After

stirring at ambient temperature for 1 hour, to the solution was added triethyl phosphonoacetate (1.9 ml) and the mixture was heated to reflux for 5 hours. After cooling to ambient temperature, to the mixture was added acetic acid (0.53 ml) and evaporated. The residue was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel (200 ml) eluting with mixture of n-hexane and diisopropyl ether (99:1–20:1, V/V) to give Ethyl (E)-3-[4-(4-heptylphenyl)phenyl]-2-butenoate (2.19 g).

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.13–1.48 (8H, m), 1.48–1.78 (2H, m), 2.61 (3H, s), 2.65 (2H, t, J=7.4 Hz), 4.22 (2H, q, J=7.1 Hz), 6.20 (1H, t, J=2.7 Hz), 7.23–7.28 (2H, m), 7.50–7.63 (6H, m)

APCI-MASS: m/s=365 (M^++1)

Preparation 311

To a solution of 4-bromo-4'-n-heptylbiphenyl (5.1 g) in tetrahydrofuran (60 ml) was added a solution of n-butyllithium in a mixture of n-hexane and diethyl ether (1.6M, 9.7 ml) at −60° C. After stirring at −60° C. for 30 minutes, to the mixture was added N,N-dimethylacetamide (4.3 ml) and the reaction mixture was allowed to warm to 0° C. The reaction mixture was taken up into a mixture of cold water and ethyl acetate, and the pH was adjusted to around 1 with 1N hydrochloric acid. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel (150 ml) eluting with a mixture of n-hexane and ethyl acetate (20:1, V/V) to give 4-Acetyl-4'-n-heptylbiphenyl (1.60 g).

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.6 Hz), 1.05–1.48 (8H, m), 1.48–1.75 (2H, m), 2.65 (2H, t, J=7.6 Hz), 2.63 (3H, s), 7.20–7.31 (2H, m), 7.52–7.58 (2H, m), 7.65–7.70 (2H, m), 7.97–8.05 (2H, m)

APCI-MASS: m/z=295 (M+1)

Preparation 312

To a solution of Methyl 4-[4-(8-hydroxyoctyloxy)phenyl] benzoate (500 mg) and dihydropyran (141 mg) in dichloromethane (15 ml) was added p-toluenesulfonic acid (5 ml). The mixture was stirred at ambient temperature for 10 minutes and diluted with dichloromethane and washed with water and brine. The separated organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give Methyl 4-[4-(8-tetrahydropyran-2-yl-oxyoctyloxy) phenyl]benzoate (616 mg).

IR (KBr): 2935, 2856, 1722, 1602, 1438, 1290, 1199 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–2.0 (18H, m), 3.3–3.9 (4H, m), 3.93 (3H, s), 4.00 (2H, t, J=6.5 Hz), 4.5–4.6 (1H, m), 6.98 (2H, d, J=8.7 Hz), 7.56 (2H, d, J=8.7 Hz), 7.62 (2H, d, J=8.3 Hz), 8.07 (2H, d, J=8.3 Hz)

Preparation 313

To a solution of titanium(IV) chloride (11.6 g) in dichloromethane (100 ml) was added 4-n-Pentyloxyacetophenone (10.3 g) and Methyl 4-formylbenzoate (8.21 g) in dichloromethane (50 ml) dropwise at 0° C. To the mixture was added triethylamine (11.15 ml) in dichloromethane (30 ml). The mixture was stirred at 0° C. for 30 minutes and diluted with n-hexane. The organic layer was washed with water (four times), brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was triturated with iso-propyl ether. The solid was collected by filtration and dried to give 1-(4-Methoxycarbonylphenyl)-3-(4-n-pentyloxyphenyl)-1-propen-3-one (4.02 g).

IR (KBr): 2950, 2910, 2863, 1718, 1654, 1606, 1274, 1176 cm^{-1} NMR ($CDCl_3$, δ): 0.94 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.8–2.0 (2H, m), 3.93 (3H, s), 4.04 (2H, t, J=6.5 Hz), 6.97 (2H, d, J=8.8 Hz), 7.60 (1H, d, J=15.7 Hz), 7.68 (2H, d, J=8.4 Hz), 7.80 (1H, d, J=15.7 Hz), 8.0–8.2 (4H, m) APCI-MASS: m/z=353 ($M+H^+$)

Preparation 314

To a solution of titanium(IV) chloride (13.88 g) in dichloromethane (100 ml) was added Ethyl 4-acetylbenzoate (11.53 g) and 4-n-pentyloxybenzaldehyde (12.68 g) in dichloromethane (50 ml) was added dropwise at 0° C. To the mixture was added triethylamine (12.44 ml) in dichloromethane (30 ml). The mixture was stirred at 0° C. for 30 minutes and diluted with ethyl acetate. The organic layer was washed with water (four times) and brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was triturated with n-hexane. The solid was collected by filtration and dried to give 1-(4-n-Pentyloxyphenyl)-3-(4-ethoxycarbonylphenyl)-1-propen-3-one (13.45 g).

IR (KBr): 2956, 2929, 2861, 1718, 1656, 1594, 1510, 1272 cm^{-1} NMR ($CDCl_3$, δ): 0.94 (3H, t, J=7.1 Hz), 1.3–1.9 (9H, m), 4.01 (2H, t, J=6.5 Hz), 4.42 (2H, q, J=7.1 Hz), 6.93 (1H, d, J=8.7 Hz), 7.37 (1H, d, J=15.6 Hz), 7.60 (2H, d, J=8.7 Hz), 7.81 (1H, d, J=15.6 Hz), 8.03 (2H, d, J=8.5 Hz), 8.16 (2H, d, J=8.5 Hz) APCI-MASS: m/z=367 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 314.

Preparation 315

Ethyl 4-oxo-1-(4-n-hexyloxyphenyl)piperidine-3-carboxylate

IR (Neat): 1664.3, 1511.9, 1243.9, 1216.9 cm^{-1} NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.5 (6H, m), 1.32 (3H, t, J=7.1 Hz), 1.65–1.85 (2H, m), 2.51 (2H, t, J=5.8 Hz), 3.31 (2H, t, J=5.8 Hz), 3.76 (2H, s), 3.91 (2H, t, J=6.5 Hz), 4.26 (2H, q, J=7.1 Hz), 6.84 (2H, d, J=9.2 Hz), 6.94 (2H, d, J=9.2 Hz), 12.06 (1H, s) APCI-MASS: m/z=348 (M^++H)

Preparation 316

To a solution of 4-n-Hexyloxybenzoylhydrazine (1.96 g) and pyridine (0.74 ml) in tetrahydrofuran (20 ml) was added a solution of terephthalic acid monomethyl ester chloride (1.56 g) in tetrahydrofuran (15 ml) dropwise at 0° C. The reaction mixture was stirred at room temperature for 2 hours, and poured into water. The precipitate was collected by filtration and washed with acetonitrile. The residue was dried under reduced pressure to give 1-(4-n-Hexyloxybenzoyl)-2-(4-methoxycarbonylbenzoyl) hydrazine (2.99 g).

IR (KBr): 3230, 3023, 2954, 2858, 1724, 1681, 1643, 1280, 1251, 1105 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 3.90 (3H, s), 4.04 (2H, t, J=6.4 Hz), 7.04 (2H, d, J=8.7 Hz), 7.90 (2H, d, J=8.7 Hz), 8.03 (2H, d, J=8.4 Hz), 8.10(2H, d, J=8.4 Hz), 10.42 (1H, s), 10.65 (1H, s) APCI-MASS: m/z=399 $M+H)^+$

Preparation 317

A mixture of 1-(4-n-Hexyloxyphenyl)-4-piperidone (0.823 g), 1-(4-Ethoxycarbonylphenyl)piperazine (0.7 g),

and titanium(IV) isopropoxide (1.11 ml) was stirred at room temperature. After 1 hour, the IR spectrum of the mixture showed no ketone band, and the viscous solution was diluted with absolute ethanol (3 ml). Sodium cyanoborohydride (0.121 g) was added, and the solution was stirred for 3 hours. Water (3 ml) was added with stirring, and the resulting in organic precipitate was filtered and washed with ethanol. The filtrate was extracted with ethyl acetate. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure to give Ethyl 4-[4-[1-(4-n-hexyloxyphenyl)piperidin-4-yl]piperazine-1-yl]benzoate (331 mg).

IR (KBr): 1708.6, 1606.4, 1511.9, 1284.4, 1236.1 cm^{-1} NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.55 (6H, m), 1.37 (3H, t, J=7.1 Hz), 1.6–1.85 (4H, m), 1.95 (2H, d, J=12 Hz), 2.41 (1H, m), 2.62 (2H, d, J=11 Hz), 2.75 (4H, t, J=5.0 Hz), 3.35 (4H, t, J=5.0 Hz), 3.58 (2H, d, J=11 Hz), 3.90 (2H, t, J=6.5 Hz), 4.32 (2H, q, J=7.1 Hz), 6.7–7.0 (6H, m), 7.92 (2H, d, J=9.0 Hz) APCI-MASS: m/z=494 (M^++H)

The following compound was obtained according to a similar manner to that of Preparation 317.

Preparation 318

1-tert-Butoxycarbonyl-4-(4-phenylcyclohexyl)piperazine

IR (KBr): 1697.1, 1245.8, 1170.6, 1124.3, 700 cm^{-1} NMR ($CDCl_3$, δ): 1.2–1.65 (17H, m), 1.9–2.1 (4H, m), 2.3–2.6 (2H, m), 2.55 (4H, t, J=5.0 Hz), 3.44 (4H, t, J=5.0 Hz), 7.1–7.4 (5H, m) APCI-MASS: m/z=345 (M^++H)

Preparation 319

To a suspension of 1-(N,N-dimethylamino)-2-(4-ethoxycarbonylbenzoyl)ethylene (0.742 g) and 4-n-hexyloxybenzamidine hydrochloride (0.847 g) in methanol (10 ml) was added 28% sodium methoxide in methanol (0.64 ml). The suspension was refluxed for 6 hours, and partitioned with ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with acetonitrile, collected by filtration and dried under reduced pressure to give Methyl 4-[2-(4-n-hexyloxyphenyl)pyrimidin-6-yl]benzoate (0.61 g).

IR (KBr): 2931, 2861, 1722, 1606, 1588, 1251 cm^{-1} NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.7 Hz), 1.2–1.6 (6H, m), 1.8–2.0 (2H, m), 3.97 (3H, s), 4.05 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.8 Hz), 7.56 (1H, d, J=5.2 Hz), 8.18 (2H, d, J=8.6 Hz), 8.28 (2H, d, J=8.6 Hz), 8.52 (2H, d, J=8.8 Hz), 8.83 (1H, d, J=5.2 Hz) APCI-MASS: m/z=391 ($M+H^+$)

Preparation 320

A solution of 1-(4-Methoxycarbonylphenyl)-3-(4-n-pentyloxyphenyl)-1-propen-3-one (4.0 g) and hydroxyamine hydrochloride (3.93 g) in ethanol (40 ml) was refluxed for 4 hours. The mixture was diluted with ethyl acetate, and the organic layer was washed with water (×2), brine and dried over magnesium sulfate. The solvents were removed under reduced pressure to give crude oxime. To a solution of crude oxime in 1,2-dichloroethane (20 ml) was added activated-manganese(IV) oxide (10.0 g). The reaction mixture was refluxed for 2 hours and filtered. The residue was washed with dichloromethane. The solvents were removed under reduced pressure and the residue was triturated with acetonitrile. The solid was collected by filtration and dried to give Methyl 4-[3-(4-n-pentyloxyphenyl) isoxazol-5-yl]benzoate (0.98 g).

IR (KBr): 2940, 2871, 1720, 1612, 1278, 1249, 1178, 1108 cm^{-1} NMR (DMSO-d_6, δ): 0.94 (3H, t, J=7.2 Hz), 1.2–1.6 (4H, m), 1.7–1.9 (2H, m), 3.95 (3H, s), 4.01 (2H, t, J=6.5 Hz), 6.87 (1H, s), 6.98 (2H, d, J=8.9 Hz), 7.79 (2H, d, J=8.9 Hz), 7.89 (2H, d, J=8.6 Hz), 8.15 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=366 ($M+H^+$)

Preparation 321

To a solution of 4-Methoxycarbonylphenylhydroxyiminomethyl chloride (16.98 g) and 4-n-pentyloxyphenylacetylene (18.96 g) in tetrahydrofuran (170 ml) was added triethylamine (14.4 ml) in tetrahydrofuran (140 ml) over a period of 2 hours at 40° C. and the mixture was stirred at 40° C. for 30 minutes. The mixture was diluted with dichloromethane and washed with water and brine. The separated organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with acetonitrile. The precipitate was collected by filtration and dried to give Methyl 4-[5-(4-n-pentyloxyphenyl)isoxazol-3-yl]benzoate (24.56 g).

IR (KBr): 2942, 2873, 1716, 1616, 1508, 1280, 1108 cm^{-1} NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.8–2.0 (2H, m), 3.95 (3H, s), 4.02 (2H, t, J=6.5 Hz), 6.74 (1H, s), 6.99 (2H, d, J=8.8 Hz), 7.76 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.5 Hz), 8.14 (2H, d, J=8.5 Hz) APCI-MASS: m/z=366 ($M+H^+$)

Preparation 322

To a solution of N-Hydroxy-4-octyloxybenzamidine (1.89 g) in pyridine (10 ml) was added terephthalic acid monomethyl ester chloride (1.67 g) in tetrahydrofuran (15 ml) dropwise at 0° C. The mixture was stirred at room temperature for 15 minutes, and poured into water. The precipitate was collected by filtration, dried and dissolved in pyridine (10 ml). The solution was refluxed for 1 hour. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl, water and brine. The separated organic layer was dried over magnesium sulfate and the solvents were removed under reduced pressure. The residue was triturated with acetonitrile and collected by filtration. The solid was dried to give Methyl 4-[3-(4-n-hexyloxyphenyl)-1,2,4-oxadiazol-5-yl]benzoate (2.27 g).

IR (KBr): 2950, 2925, 2863, 1720, 1280, 1255 cm^{-1} NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.6 Hz), 1.2–1.9 (8H, m), 3.97 (3H, s), 4.03 (2H, d, J=6.5 Hz), 7.00 (2H, d, J=8.9 Hz), 8.09 (2H, d, J=8.9 Hz), 8.20 (2H, d, J=6.6 Hz), 8.28 (2H, d, J=6.6 Hz) APCI-MASS m/z=381 $(M+H)^+$

Preparation 323

A suspension of 1-(4-n-Hexyloxybenzoyl)-2-(4-methoxycarbonylbenzoyl)hydrazine (1.00 g) in phosphorus oxychloride (5 ml) was refluxed for 1 hour. After cooling, the solution was concentrated under reduced pressure. The residue was poured into ice-water and extracted with dichloromethane. The organic layer was washed with water, brine and dried over magnesium sulfate. The solvents were removed under reduced pressure. The residue was triturated with acetonitrile, collected by filtration and dried under reduced pressure to give Methyl 4-[5-(4-n-hexyloxyphenyl)-1,3,4-oxadiazole-2-yl]benzoate (761 mg).

IR (KBr): 2954, 2854, 1724, 1612, 1494, 1280, 1249 cm^{-1} NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.6 Hz), 1.3–1.6 (6H, m), 1.7–1.9 (2H, m), 3.96 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.6 Hz), 8.07 (2H, d, J=8.6 Hz), 8.19 (4H, m) APCI-MASS: m/z=381 $(M+H)^+$

The following compounds (Preparations 324 to 327) were obtained according to a similar manner to that of Preparation 323.

Preparation 324

Methyl 4-[5-[4-(4-n-propyloxyphenyl)phenyl]-1,3,4-oxadiazol-2-yl]benzoate

IR (KBr): 1720, 1614, 1496, 1280, 1103 cm^{-1} NMR ($CDCl_3$, δ): 1.07 (3H, d, J=7.5 Hz), 1.84 (2H, tq, J=6.5 and 7.5 Hz), 3.98 (3H, s), 3.99 (2H, t, J=6.5 Hz), 7.01 (2H, d, J=8.8 Hz), 7.60 (2H, d, J=8.8 Hz), 7.73 (2H, d, J=8.5 Hz), 8.19 (2H, d, J=8.5 Hz), 8.22 (4H, s) APCI-MASS: m/z=415 ($M+H^+$)

Preparation 325

Methyl 4-[5-(n-nonyl)-1,3,4-oxadiazol-2-yl]benzoate

IR (KBr): 2915, 2848, 1724, 1569, 1436, 1413, 1278 cm^{-1} NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.4 Hz), 1.2–1.6 (12H, m), 1.8–2.0 (2H, m), 2.94 (2H, t, J=7.6 Hz), 3.96 (3H, s), 8.11 (2H, d, J=8.8 Hz), 8.17 (2H, d, J=8.8 Hz) APCI-MASS: m/z=331 $(M+H)^+$

Preparation 326

Methyl 4-[5-[4-(8-methoxyoctyloxy)phenyl]-1,3,4-oxadiazol-2-yl]benzoate

IR (KBr): 2925, 2858, 1722, 1614, 1280, 1259 cm^{-1} NMR ($CDCl_3$, δ): 1.3–1.9 (12H, m), 3.36 (3H, s), 3.37 (2H, t, J=6.4 Hz), 3.97 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.9 Hz), 8.07 (2H, d, J=8.9 Hz), 8.20 (4H, s) APCI-MASS: m/z=439 ($M+H^+$)

Preparation 327

Methyl 4-[5-(4-n-octyloxyphenyl)-1,3,4-oxadiazol-2-yl]benzoate

IR (KBr): 2923, 2856, 1722, 1614, 1496, 1282, 1103 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.97 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.03 (2H, d, J=8.7 Hz), 8.07 (2H, d, J=8.7 Hz), 8.19 (4H, m) APCI-MASS: m/z=409 ($M+H^+$)

Preparation 328

A suspension of 1-(4-Hexyloxybenzoyl)-2-(4-methoxycarbonylbenzoyl)hydrazine (1.0 g) and di-phosphorus pentasulfide (1.28 g) in tetrahydrofuran (15 ml) was stirred at room temperature for 3 hours. The mixture was diluted with water (30 ml), stirred for 30 minutes and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with acetonitrile. The solid was collected by filtration and dried under reduced pressure to give Methyl 4-[5-(4-n-hexyloxyphenyl)-1,3,4-thiadiazol-2-yl]benzoate (816 mg).

IR (KBr): 2925, 2871, 1722, 1608, 1436, 1276, 1106 cm^{-1} NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.6 Hz), 1.3–2.0 (8H, m), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 6.99 (2H, d, J=8.6 Hz), 7.95 (2H, d, J=8.4 Hz), 8.16 (2H, d, J=8.4 Hz) APCI-MASS: m/z=397 $(M+H)^+$

The following compounds (Preparations 329 to 334) were obtained according to a similar manner to that of Preparation 328.

Preparation 329

Methyl 4-[5-[4-(8-methoxyoctyloxy)phenyl]-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 3210, 2935, 2856, 1718, 1600, 1465, 1280, 1110 cm^{-1} NMR ($CDCl_3$, δ): 1.3–1.6 (10H, m), 1.7–1.9 (2H, m), 3.33 (3H, s), 3.37 (2H, d, J=6.4 Hz), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 6.99 (2H, d, J=8.9 Hz), 7.94 (2H, d, J=8.9 Hz), 8.07 (2H, d, J=8.6 Hz), 8.16 (2H, d, J=8.6 Hz) APCI-MASS: m/z=455 ($M+H^+$)

Preparation 330

Methyl 4-[5-(4-cyclohexylphenyl)-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 2925, 2850, 1716, 1432, 1274, 1108, 997 cm^{-1} NMR ($CDCl_3$, δ): 1.2–1.6 (5H, m), 1.7–2.0 (5H, m), 2.58 (1H, m), 3.96 (3H, s), 7.34 (2H, d, J=8.2 Hz), 7.93 (2H, d, J=8.2 Hz), 8.07 (2H, ,d, J=8.6 Hz), 8.16 (2H, d, J=8.6 Hz) APCI-MASS: m/z=379 ($M+H^+$)

Preparation 331

Methyl 4-[5-[4-(piperidin-1-yl)phenyl]-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 2940, 2848, 1720, 1602, 1436, 1415, 1276, 1108 cm^{-1} NMR ($CDCl_3$, δ): 1.68 (6H, br), 3.34 (4H, br), 3.96 (3H, s), 6.95 (2H, d, J=8.7 Hz), 7.88 (2H, d, J=8.7 Hz), 8.05 (2H, d, J=8.6 Hz), 8.16 (2H, d, J=8.6 Hz) APCI-MASS: m/z=380 ($M+H^+$)

Preparation 332

Methyl 4-[5-(4-n-octyloxyphenyl)-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 2927, 2858, 1720, 1606, 1434, 1276, 1106 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 7.00 (2H, d, J=8.9 Hz), 7.95 (2H, d, J=8.9 Hz), 8.06 (2H, d, J=8.4 Hz), 8.16 (2H, d, J=8.4 Hz) APCI-MASS: m/z=425 ($M+H^+$)

Preparation 333

Methyl 4-[5-(4-trans-n-pentylcyclohexyl)-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 2923, 2850, 1722, 1440, 1276, 1110 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.9 Hz), 1.0–1.8 (13H, m), 1.92 (2H, d, J=13.4 Hz), 2.24 (2H, d, J=12.2 Hz), 3.15 (1H, tt, J=12.2 and 3.5 Hz), 3.95 (3H, s), 8.01 (2H, dd, J=8.6 and 2.0 Hz), 8.13 (2H, dd, J=8.6 and 2.0 Hz) APCI-MASS: m/z=373 ($M+H^+$)

Preparation 334

Methyl 4-[5-[4-(4-n-propyloxyphenyl)phenyl]-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 1720, 1540, 1508, 1282 cm^{-1} NMR ($CDCl_3$, δ): 1.07 (3H, t, J=7.5 Hz), 1.85 (2H, m), 3.9–4.1 (5H, m), 7.01 (2H, d, J=8.8 Hz), 7.59 (2H, d, J=8.8 Hz), 7.70 (2H, d, J=8.4 Hz), 8.07 (2H, d, J=8.4 Hz), 8.1–8.2 (4H, m) APCI-MASS: m/z=431 $(M+H)^+$

Preparation 335

To a suspension of 4-hexyloxybenzoic acid in oxalyl chloride (10 ml) and dichloromethane (10 ml) was added N,N-dimethylformamide (0.1 ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to give crude 4-hexyloxybenzoyl chloride. To a suspension of Ethyl 3-amino-4-

hydroxybenzoate (733 mg) and triethylamine (1.38 ml) and 4-dimethylaminopyridine (DMAP, 10 mg) in methylene chloride (10 ml) was added the solution of 4-hexyloxybenzoyl chloride obtained above in dichloromethane (5 ml) dropwise at 10° C. The reaction mixture was stirred at 10° C. for 1.5 hours and diluted with dichloromethane (20 ml). The solution was washed with H_2O (20 ml), 1 N HCl aq. (20 ml×2), H_2O (20 ml) and brine (20 ml) successively. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. To the residue was added toluene (15 ml) and p-toluenesulfonic acid (10 mg). The mixture was refluxed for 6 hours and the solvent was removed under reduced pressure. The residue was triturated with acetonitrile, and precipitate was collected with filtration and dried over PO_5 to give 2-(4-Hexyloxyphenyl)-5-ethoxycarbonylbenzoxazole (0.60 g).

IR (KBr): 2952, 2871, 1712, 1623, 1500, 1294, 1255 cm^{-1} NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.6 Hz), 1.3–1.6 (9H, m), 1.7–1.9 (2H, m), 4.05 (2H, t, J=6.5 Hz), 4.42 (2H, q, J=7.1 Hz), 7.03 (2H, d, J=6.9 Hz), 7.57 (1H, d, J=8.6 Hz), 8.08 (1H, dd, J=8.6 and 1.7 Hz), 8.18 (2H, d, J=6.9 Hz), 8.43 (1H, d, J=1.7 Hz) APCI-MASS: m/z=368 ($M+H^+$)

The following compounds (Preparations 336 to 337) were obtained according to a similar manner to that of Preparation 335.

Preparation 336

5-Ethoxycarbonyl-2-(2-octyloxypyridin-5-yl) benzoxazole

IR (KBr): 2933, 2858, 1716, 1623, 1604, 1577, 1467, 1290, 1213, 1083 cm^{-1} NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.43 (3H, t, J=7.1 Hz), 1.7–1.9 (2H, m), 4.3–4.5 (4H, m), 6.87 (1H, d, J=8.7 Hz), 7.60 (1H, d, J=8.6 Hz), 8.11 (1H, dd, J=8.6 and 1.6 Hz), 8.37 (1H, dd, J=8.8 and 2.4 Hz), 8.45 (1H, d, J=1.6 Hz), 9.03 (1H, d, J=2.4 Hz) APCI-MASS: m/z=397 ($M+H^+$)

Preparation 337

2-[4-(4-hexylphenyl)phenyl]-5-ethoxycarbonylbenzoxazole

IR (KBr): 2952, 2871, 1712, 1623, 1500, 1294, 1255, 1024 cm^{-1} NMR ($CDCl_3$, δn): 0.90 (3H, t, J=6.6 Hz), 1.2–1.5 (6H, m), 1.44 (3H, t, J=7.1 Hz), 1.6–1.8 (2H, m), 2.67 (2H, t, J=7.3 Hz), 4.43 (2H, q, J=7.1 Hz), 7.27 (1H, d, J=3.7 Hz), 7.32 (1H, s), 7.5–7.7 (3H, m), 7.77 (2H, d, J=8.6 Hz), 8.12 (1H, dd, J=8.6 and 1.7 Hz), 8.32 (2H, d, J=8.5 Hz), 8.48 (1H, d, J=1.2 Hz) APCI-MASS: m/z=428 ($M+H^+$)

Preparation 338

A suspension of 4-[4-(8-bromooctyloxy)phenyl]benzoic acid (1 g) in 2,6-dimethylmorpholine (3.06 ml) was refluxed for 30 minutes. The reaction mixture was added to a mixture of water and ethyl acetate and adjusted to pH 2.0 with conc. HCl. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-[8-(2,6-dimethylmorpholin-4-yl)octyloxy]phenyl] benzoic acid hydrochloride (0.95 g).

IR (KBr): 2939.0, 1704.8, 1606.4, 1189.9 cm^{-1} NMR (DMSO-d_6, δ): 1.12 (6H, d, J=6.3 Hz), 1.2–1.6 (10H, m), 1.6–1.9 (4H, m), 2.4–2.7 (2H, m), 2.9–3.1 (2H, m), 3.8–4.0 (2H, m), 4.02 (2H, t, J=6.3 Hz), 7.04 (2H, d, J=8.8 Hz), 7.68 (2H, d, J=8.8 Hz), 7.75 (2H, d, J=8.4 Hz), 7.99 (2H, d, J=8.4 Hz) APCI-MASS: m/z=440 ($M+H^+$)

Preparation 339

Sodium hydride (60% suspension in mineral oil, 108 mg) was added to ethoxyethanol (10 ml), and the solution was stirred at 60° C. for 20 minutes. To the solution was added Methyl 4-[4-(8-bromooctyloxy)phenyl]benzoate (1.26 g), and the reaction mixture was stirred at 70° C. for 2 hours. To the reaction mixture was added 10% sodium hydroxide aqueous solution (2.4 ml), and the solution was stirred at 70° C. for 1 hour. After cooling, the solution was adjusted to pH 2.0 with 1 N hydrochloric acid. The precipitate was collected by filtration, and dried to give 4-[4-[8-(2-Ethoxyethoxy) octyloxy]phenyl]benzoic acid (1.13 g).

IR (KBr): 2933, 2858, 1685, 1604, 1434, 1294, 1132 cm^{-1} NMR (DMSO-d_6, δ): 1.09 (3H, t, J=7.0 Hz), 1.2–1.9 (14H, m), 3.2–3.6 (6H, m), 4.01 (2H, d, J=6.3 Hz), 7.04 (2H, d, J=8.8 Hz), 7.67 (2H, d, J=8.8 Hz), 7.74 (2H, d, J=8.5 Hz), 7.98 (2H, d, J=8.5 Hz) APCI-MASS: m/z=415 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 300.

Preparation 340

4-n-Pentyloxybenzoylhydrazine

IR (KBr): 3182, 2937, 2869, 1645, 1618, 1571, 1251 cm^{-1} NMR (DMSO-d_6, δ): 0.89 (3H, d, J=7.1 Hz), 1.2–1.8 (6H, m), 4.00 (2H, t, J=6.5 Hz), 4.41 (2H, s), 6.96 (2H, d, J=8.8 Hz), 7.78 (2H, d, J=8.8 Hz), 9.59 (1H, s) APCI-MASS: m/z=223 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 291.

Preparation 341

1-(4-Methoxycarbonylbenzoyl)-2-(4-n-pentyloxybenzoyl)hydrazine

IR (KBr): 3234, 2956, 2931, 1724, 1683, 1643, 1610, 1284, 1253 cm^{-1} NMR (DMSO-d_6, δ): 0.90 (3H, t, J=6.9 Hz), 1.2–1.5 (4H, m), 1.6–1.8 (2H, m), 3.90 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz), 8.03 (2H, d, J=8.7 Hz), 8.10 (2H, d, J=8.7 Hz), 10.42 (1H, s), 10.64 (1H, s) APCI-MASS: m/z=385 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 328.

Preparation 342

Methyl 4-[5-(4-n-pentyloxyphenyl)thiadiazol-2-yl] benzoate

IR (KBr): 2940, 2871, 1720, 1606, 1438, 1280 cm^{-1} NMR ($CDCl_3$, δ): 0.95 (3H, t, J=7.1 Hz), 1.3–1.6 (4H, m), 1.8–2.0 (2H, m), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 6.99 (2H, d, J=8.8 Hz), 7.94 (2H, d, J=8.8 Hz), 8.06 (2H, d, J=8.7 Hz), 8.16 (2H, d, J=8.7 Hz) APCI-MASS: m/z=383 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 32

Preparation 343

4-[5-(4-n-Pentyloxyphenyl)thiadiazol-2-yl]benzoic acid

IR (KBr): 2954, 2867, 1687, 1602, 1432, 1294, 1255 cm^{-1} NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.0 Hz), 1.3–1.5 (4H, m), 1.7–1.9 (2H, m), 4.07 (2H, t, J=6.7 Hz), 7.13 (2H, d, J=8.8 Hz), 7.97 (2H, d, J=8.8 Hz), 8.07 (4H, s) APCI-MASS: m/z=369 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 49.

Preparation 344

1-[4-[5-(4-n-Pentyloxyphenyl)thiadiazol-2-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2948, 2873, 1770, 1602, 1257, 1232 cm^{-1} NMR ($CDCl_3$, δ): 0.95 (3H, t, J=7.1 Hz), 1.3–1.6 (4H, m), 1.8–2.0 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.01 (2H, d, J=8.1 Hz), 7.4–7.7 (3H, m), 7.97 (2H, d, J=8.1 Hz), 8.12 (1H, d, J=8.2 Hz), 8.24 (2H, d, J=8.0 Hz), 8.40 (2H, d, J=8.0 Hz) APCI-MASS: m/z=486 ($M+H^+$)

Preparation 345

To a solution of 4-bromobenzaldehyde oxime chloride (647 mg) and 4-n-pentyloxy-phenylacetylene (650 mg) in tetrahydrofuran (7 ml) was added triethylamine (0.5 ml) in tetrahydrofuran (5 ml) dropwise at 40° C. The solution was stirred at 40° C. for 30 minutes, poured into water and extracted with ethyl acetate. The organic layer was washed with H_2O, brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was triturated with acetonitrile. The precipitate was collected by filtration and dried to give 4-[5-(4-n-pentyloxyphenyl)isoxazol-3-yl]bromobenzene (0.59 g).

IR (KBr): 2948, 2867, 1612, 1430, 1255 cm^{-1} NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.7–1.9 (2H, m), 4.01 (2H, t, J=6.5 Hz), 6.66 (1H, s), 6.98 (2H, d, J=8.8 Hz), 7.60 (2H, d, J=8.6 Hz), 7.7–7.9 (4H, m) APCI-MASS: m/z=388 ($M+H^+$)

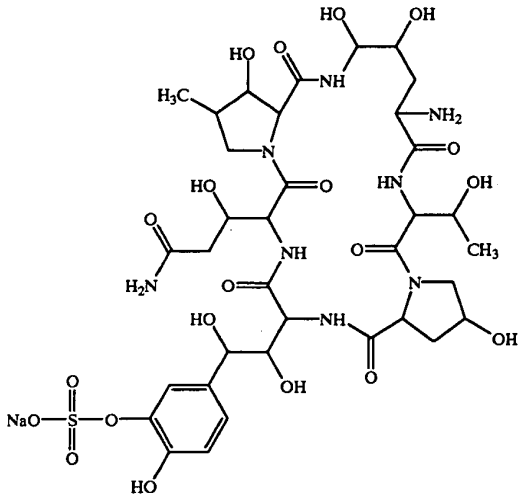
Preparation 346

To a suspension of 4-[5-(4-n-pentyloxyphenyl)isoxazol-3-yl]bromobenzene (386 mg) in tetrahydrofuran (5 ml) was added 1.55 M n-butyllithium in hexane (0.84 ml) at –40° C. under N_2 stream and the solution was stirred for 1 hour at –40° C. To the solution was added crushed dryice (1 g) and the suspension was stirred for 1 hour at –40° C. The suspension was diluted with H_2O, and acidified with 1 N-hydrochloric acid. The precipitate was collected by filtration and dried to give 4-[5-(4-n-pentyloxyphenyl) isoxazol-3-yl]benzoic acid (312 mg).

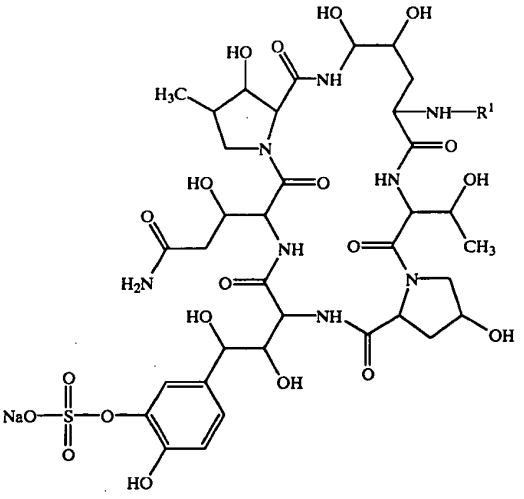
IR (KBr): 2939, 2867, 1681, 1614, 1429, 1255, 1178, 821 cm^{-1} NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.1 Hz), 1.3–1.5 (4H, m), 1.6–1.8 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.11 (2H, d, J=8.9 Hz), 7.54 (1H, s), 7.85 (2H, d, J=8.9 Hz), 7.98 (2H, d, J=8.6 Hz), 8.11 (2H, d, J=8.6 Hz) APCI-MASS: m/z=352 ($M+H^+$)

The Starting Compound in the following Examples 1 to 117 and The Object Compounds (1to (122) and (124) in the following Examples 1 to 122 and 124 are illustrated by chemical formulae as below.

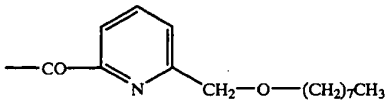
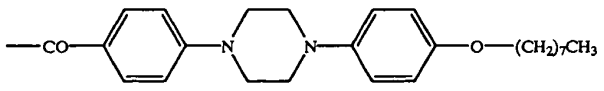
The Starting Compound (the same in Examples 1 to 117)



The Object Compounds (1) to (122) and (124)



In the following Examples, The Object Compound (X) [e.g. The Object Compound (1)] means the object compound of Example (X) [e.g. Example (1)].

Example No.	R^1
1	
2	

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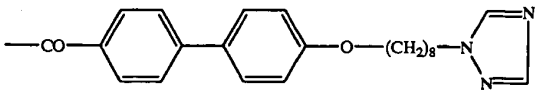

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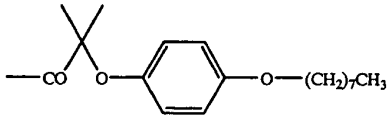

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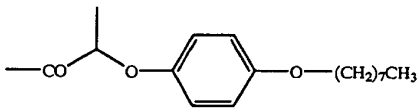

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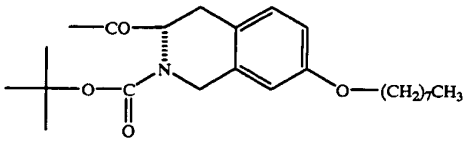

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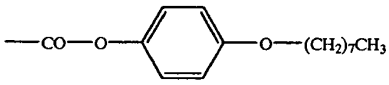

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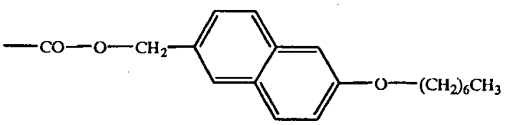

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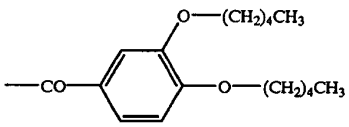

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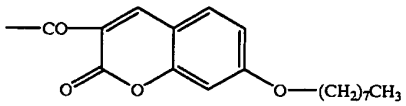

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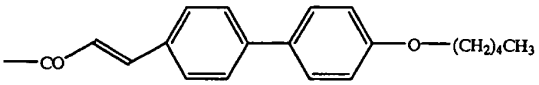

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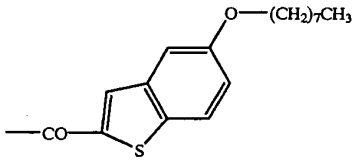

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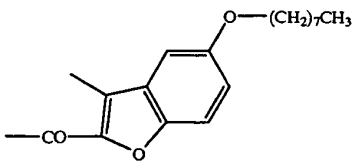

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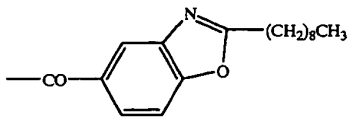

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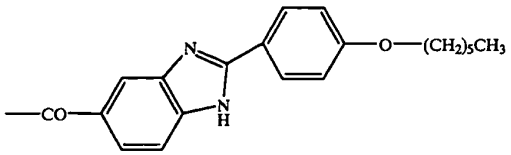

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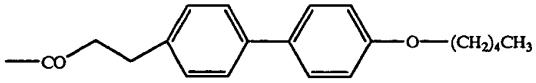

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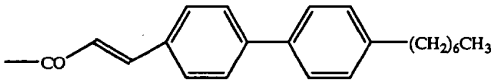

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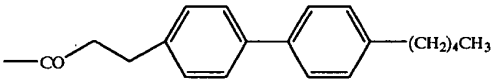

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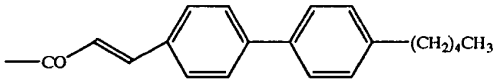

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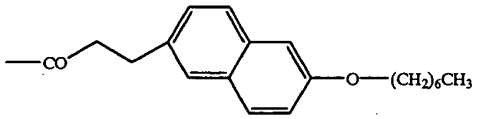

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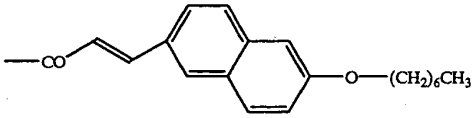

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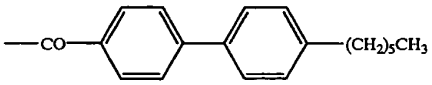

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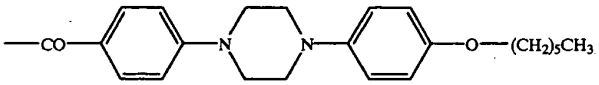

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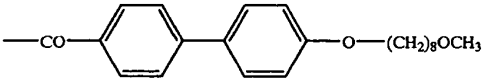

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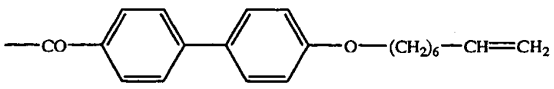

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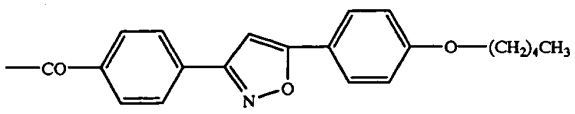

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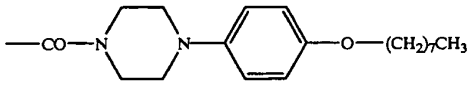

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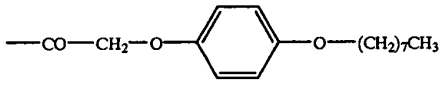

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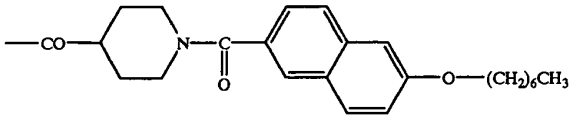

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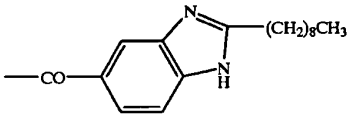

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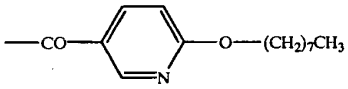

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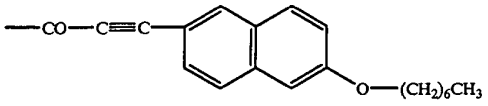

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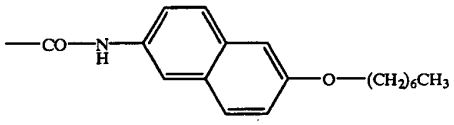

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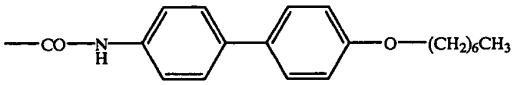

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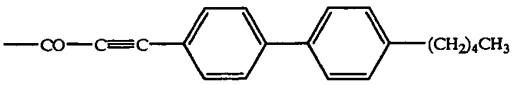

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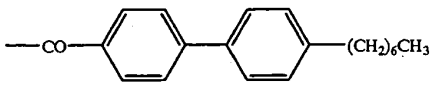

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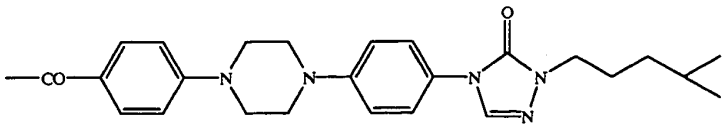

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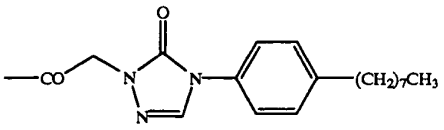

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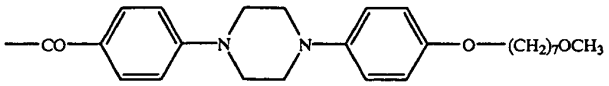

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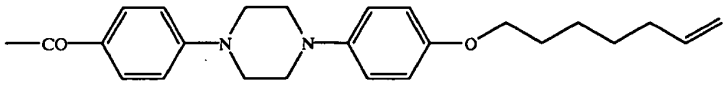

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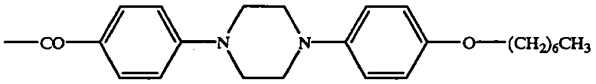

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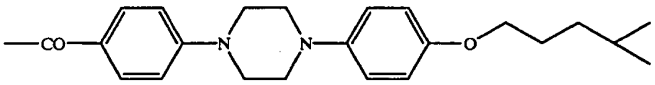

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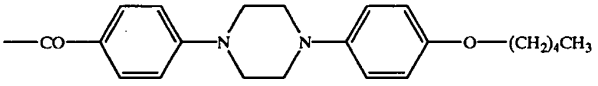

42
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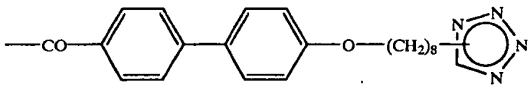

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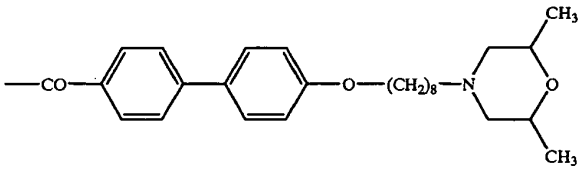

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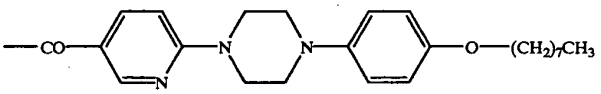

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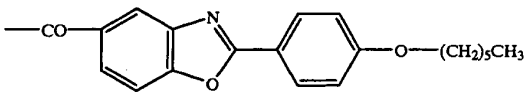

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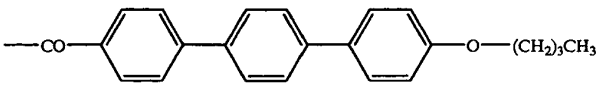

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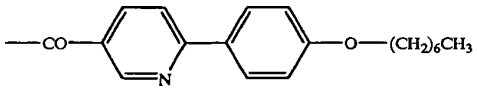

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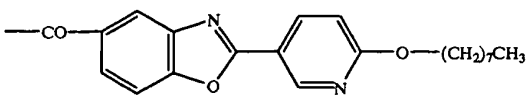

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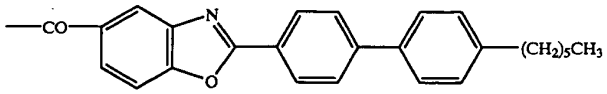

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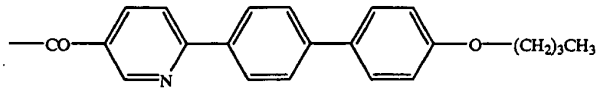

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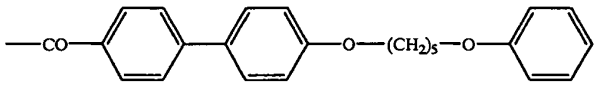

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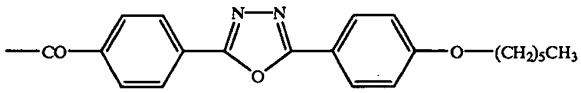

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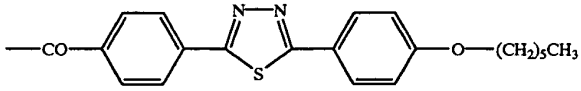

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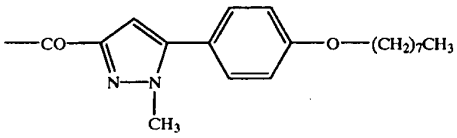

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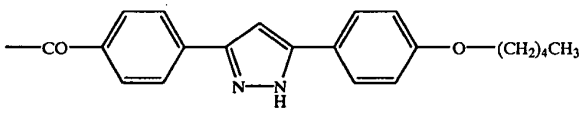

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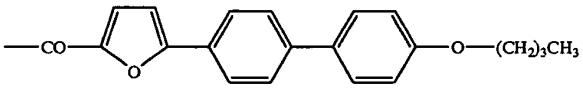

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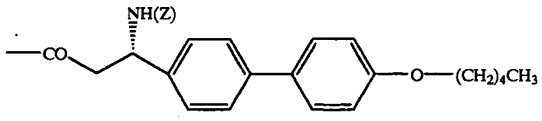

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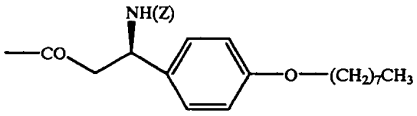

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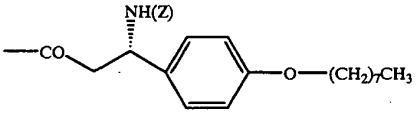

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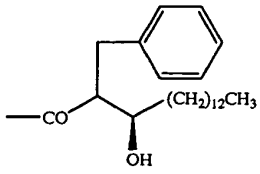

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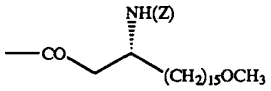

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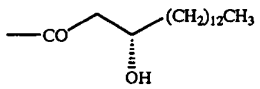

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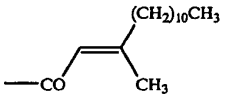

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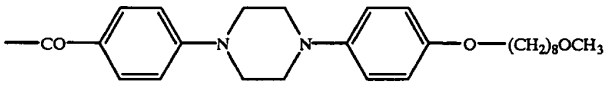

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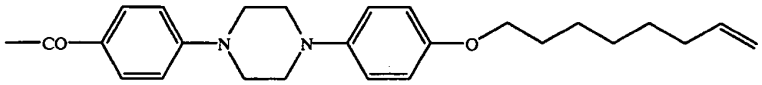

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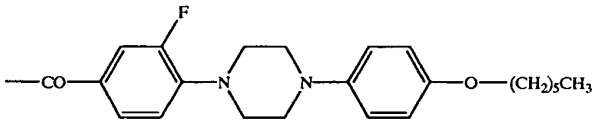

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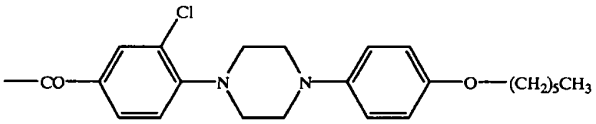

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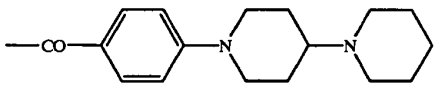

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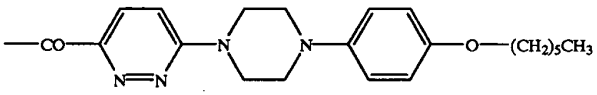

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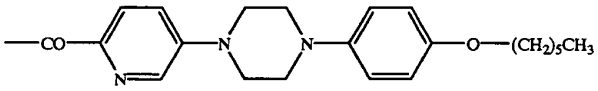

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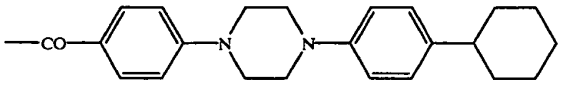

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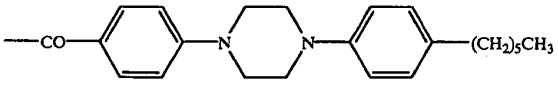

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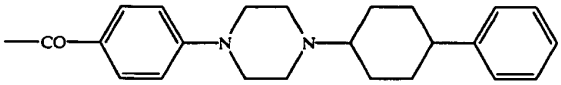

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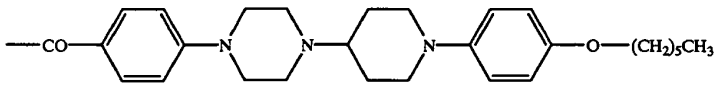
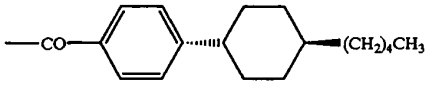
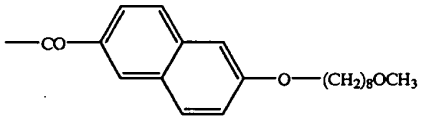
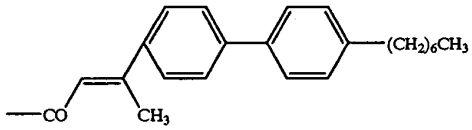
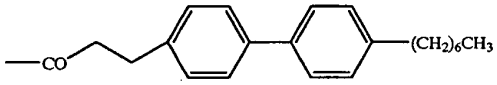
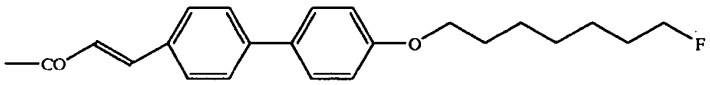
73 

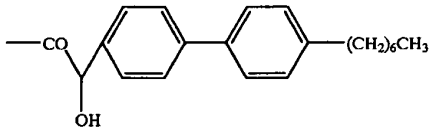
74 

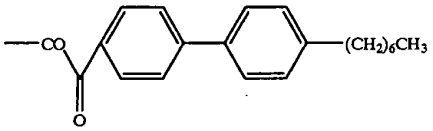
75 

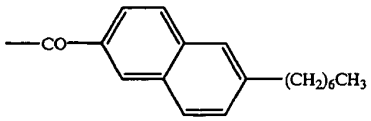
76 

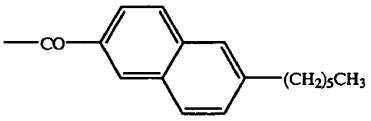
77 

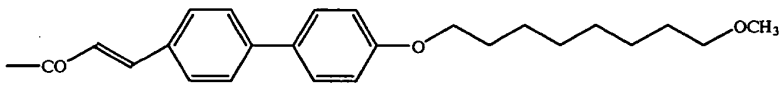
78 

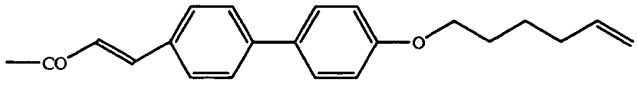
79 

80 

81 

82 

83 

84 

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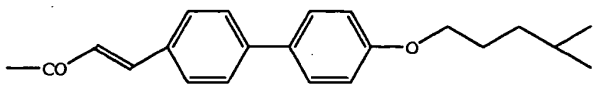
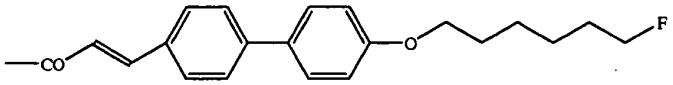
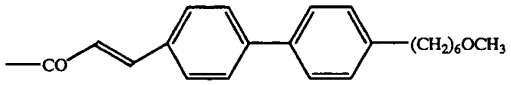
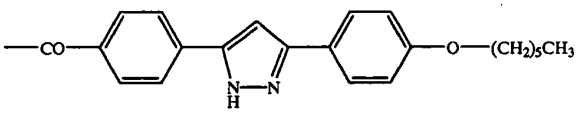
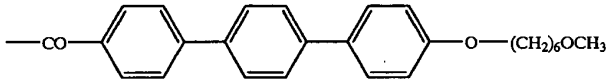
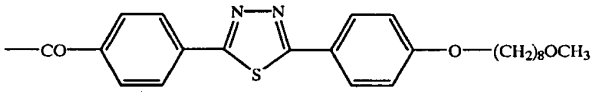
85 

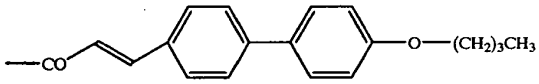
86 

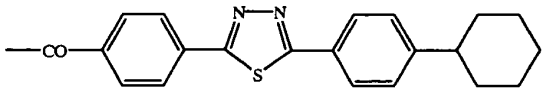
87 

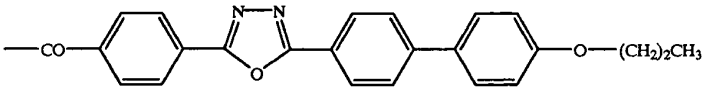
88 

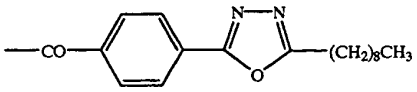
89 

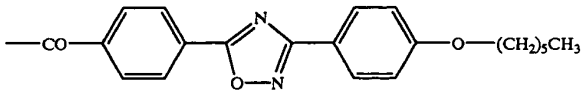
90 

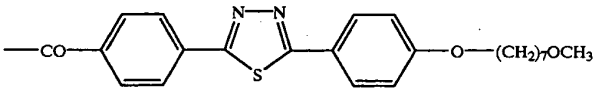
91 

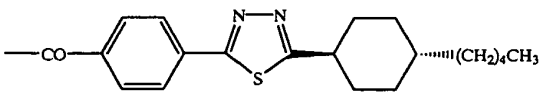
92 

93 

94 

95 

96 

97 

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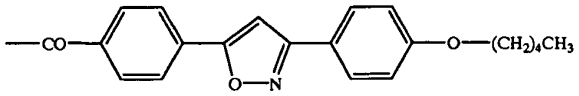

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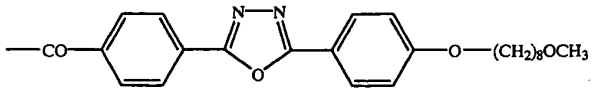

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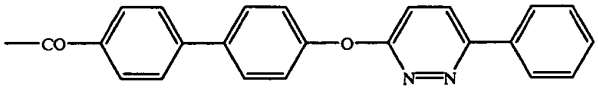

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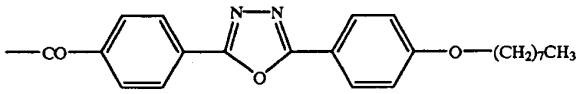

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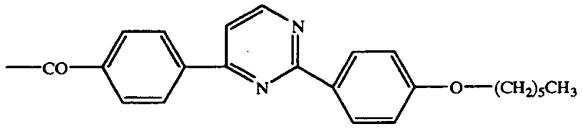

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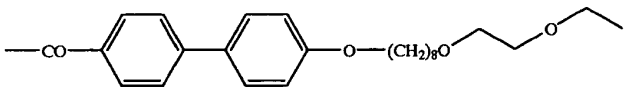

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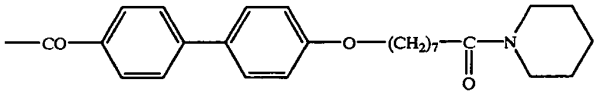

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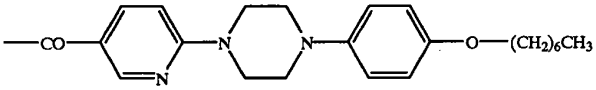

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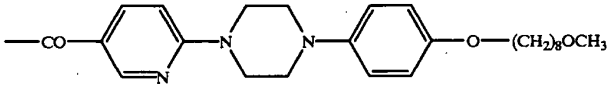

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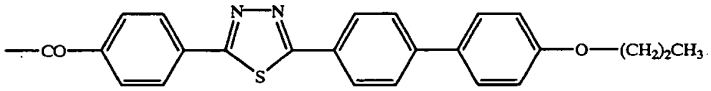

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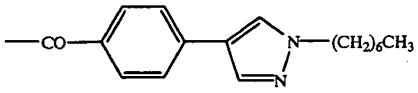

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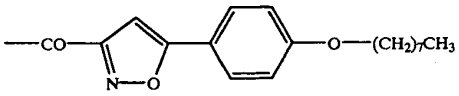

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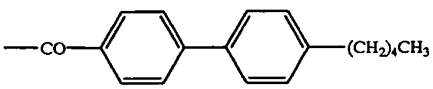

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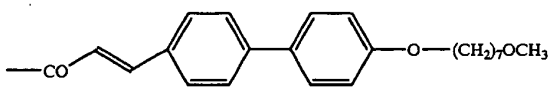
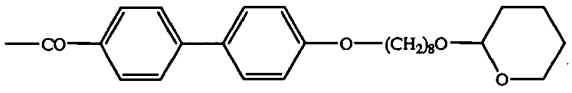
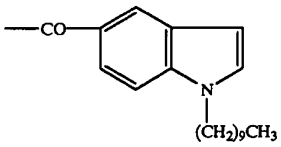
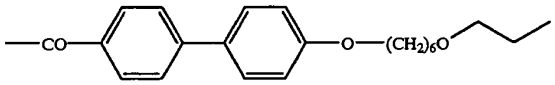
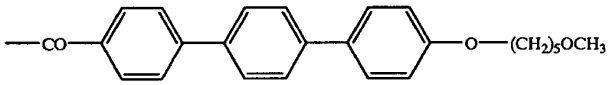
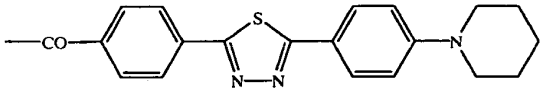
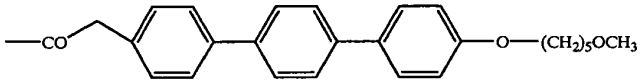
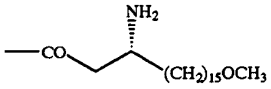
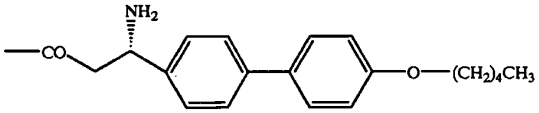
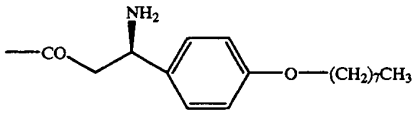
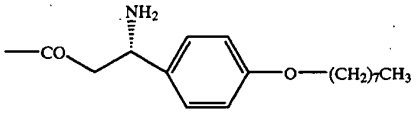
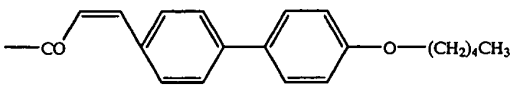
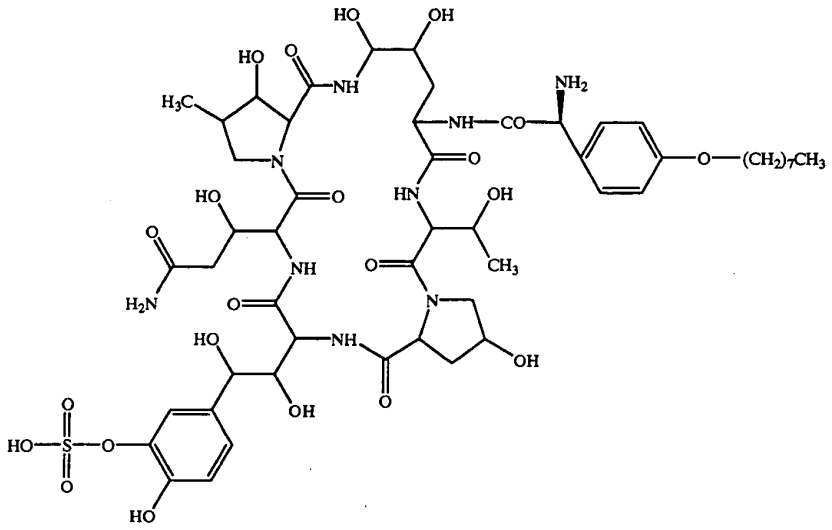
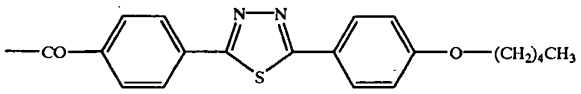
111	
112	
113	
114	
115	
116	
117	
118	
119	
120	
121	
122	

-continued

Example No.	The Object Compound
123	

Example No.	R
124	

EXAMPLE 1

To a solution of the Starting Compound (1 g) and 1-(6-octyl-oxymethylpicolinoyl)benzotriazole 3-oxide (0.399 g) in N,N-dimethylformamide (10 ml) was added 4-(N,N-dimethylamino)pyridine (0.140 g), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4 (Trademark: prepared by Dow Chemical)) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel.ODS-AM.S-50) (Trademark: prepared by Yamamura Chemical Lab.) eluting with 50% methanol aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give The Object Compound (1).

IR (KRr): 3347, 1664, 1629, 1517 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.98 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=6.0 Hz), 1.2–1.47 (10H, m), 1.47–1.67 (2H, m), 1.67–2.06 (3H, m), 2.06–2.5 (4H, m), 3.19 (1H, m), 3.53 (2H, t, J=6.4 Hz), 3.5–3.85 (2H, m), 3.85–4.7 (13H, m), 5.35 (11H, m), 5.56 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.3 Hz), 6.83 (1H, d, J=8.3 Hz), 6.89 (1H, s), 7.05 (1H, s), 7.11 (1H, s), 7.32 (1H, m), 7.43 (1H, d, J=8.5 Hz), 7.63 (1H, d, J=7.3 Hz), 7.85–8.13 (4H, m), 8.66 (1H, d, J=7.8 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1228 (M^++Na)

Elemental Analysis Calcd. for $C_{50}H_{72}N_9O_{22}SNa.6H_2O$: C 45.49, H 6.44, H 9.59 Found: C 45.89, H 6.52, N 9.69

The Object Compounds (2) to (25) were obtained according to a similar manner to that of Example 1.

EXAMPLE 2

IR (KRr): 3353, 1666, 1510, 1236 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.8 Hz), 1.2–1.5 (10H, m), 1.55–2.05 (5H, m), 2.11–2.7 (4H, m), 3.0–3.3 (5H, m), 3.3–3.5 (4H, m), 3.6–4.5 (15H, m), 4.6–5.6 (12H, m), 6.6–7.2 (10H, m), 7.2–7.5 (3H, m), 7.81 (2H, d, J=8.8 Hz), 8.05 (1H, d, J=8.7 Hz), 8.28 (1H, d, J=8.7 Hz), 8.41 (1H, d, J=6.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1373 (M^++Na)

Elemental Analysis Calcd. for $C_{60}H_{83}N_{10}O_{22}SNa.4H_2O$: C 50.63, H 6.44, H 9.84 Found: C 50.59, H 6.59, N 9.79

EXAMPLE 3

IR (KRr): 3350, 1664, 1627, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.08 (3H, d, J=5.7 Hz), 1.15–1.53 (8H, m), 1.55–2.1 (9H, m), 2.1–2.45 (3H, m), 2.5–2.7 (1H, m), 3.18 (1H, m), 3.6–3.83 (2H, m), 3.83–4.6 (17H, m), 4.7–5.4 (11H, m), 5.51 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.2 Hz), 6.85 (1H, s), 7.03 (2H, d, J=8.4 Hz), 7.05 (1H, s), 7.30 (1H, s), 7.2–7.5 (2H, m), 7.67 (2H, d, J=8.4 Hz), 7.71 (2H, d, J=7.4 Hz), 7.94 (1H, s), 7.96 (2H, d, J=7.4 Hz), 8.06 (1H, d, J=8.0 Hz), 8.25 (1H, d, J=6.7 Hz), 8.50 (1H, s), 8.74 (1H, d, J=6.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1356 (M^++Na)

Elemental Analysis Calcd. for $C_{58}H_{77}N_{11}O_{22}SNa.4H_2O$: C 49.53, H 6.02, N 10.95 Found: C 49.26, H 6.22, N 10.77

EXAMPLE 4

IR (KRr): 3350, 1660, 1631, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.9 Hz), 0.97 (3H, d, J=6.6 Hz), 1.09 (3H, d, J=5.3 Hz), 1.2–1.5 (10H, m), 1.37 (6H, s), 1.55–2.0 (5H, m), 2.1–2.6 (4H, m), 3.16 (1H, m), 3.73 (2H, m), 3.89 (2H, t, J=6.3 Hz), 3.95–4.49 (11H, m), 5.68–5.21 (10H, m), 5.25 (1H, d, J=4.1 Hz), 5.53 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz), 6.75–6.85 (4H, m), 6.91 (1H, d, J=8.2 Hz), 7.05 (1H, s), 7.15 (1H, s), 7.3–7.5 (2H, m), 7.9–8.2 (3H, m), 8.84 (1H, s)

FAB-MASS: m/z=1271 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{77}N_8O_{23}SNa.4H_2O$: C 48.18, H 6.48, H 8.48 Found: C 48.04, H 6.51, N 8.38

EXAMPLE 5

IR (KRr): 1666, 1629, 1222 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.6 Hz), 0.9–1.12 (6H, m), 1.12–1.52 (13H, m), 1.52–1.93 (5H, m), 2.08–2.55 (4H, m), 3.16 (1H, m), 3.6–5.3 (26H, m), 5.49+5.54 (1H, d, J=5.8 Hz, mixtures of diastereomer), 6.60–7.1 (7H, m), 7.04 (1H, s), 7.1 (1H, m), 7.2–7.5 (2H, m), 7.9–8.43 (3H, m), 8.83 (1H, s)

FAB-MASS: m/z=1257 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{75}N_8O_{23}SNa.3H_2O$: C 48.44, H 6.33, H 8.69 Found: C 48.16, H 6.51, N 8.53

EXAMPLE 6

IR (KBr): 3349, 1666, 1629, 1259 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.9 (3H, d, J=5.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.1–1.55 (19H, m), 1.55–2.0 (5H, m), 2.0–2.47 (4H, m), 2.65–3.25 (3H, m), 3.5–5.13 (27H, m), 5.17 (1H, d, J=3.2 Hz), 5.24 (1H, d, J=4.5 Hz), 5.38 (1H, d, J=5.9 Hz), 6.5–6.9 (5H, m), 6.9–7.1 (3H, m), 7.2–7.46 (2H, m), 7.7–8.1 (3H, m), 8.83 (1H, s)

FAB-MASS: m/z=1368 (M^++Na)

Elemental Analysis Calcd. for $C_{58}H_{84}N_9O_{24}SNa.5H_2O$: C 48.50, H 6.60, H 8.78 Found: C 48.47, H 6.83, N 8.78

EXAMPLE 7

IR (KRr): 3350, 1666, 1502, 1199 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.7 Hz), 1.2–1.5 (10H, m), 1.55–2.0 (5H, m), 2.1–2.6 (4H, m), 3.17 (1H, m), 3.7–4.5 (15H, m), 4.7–5.22 (10H, m), 5.24 (1H, d, J=4.4 Hz), 5.60 (1H, d, J=5.9 Hz), 6.68–7.03 (8H, m), 7.04 (1H, s), 7.2–7.42 (2H, m), 7.85–8.1 (3H, m), 8.83 (1H, s)

FAB-MASS: m/z=1229 (M^++Na)

Elemental Analysis Calcd. for $C_{50}H_{71}N_8O_{23}SNa.5H_2O$: C 46.29, H 6.29, H 8.64 Found: C 46.39, H 6.05, N 8.72

EXAMPLE 8

IR (KRr): 3350, 1666, 1631, 1513 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.2 Hz), 0.97 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.7 Hz), 1.2–1.58 (8H, m), 1.58–2.0 (5H, m), 2.0–2.6 (4H, m), 3.17 (1H, m), 3.6–4.5 (15H, m), 4.63–5.33 (13H, m), 5.53 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.82 (1H, d, J=8.2 Hz), 6.84 (1H, s), 6.95–7.52 (7H, m), 7.66 (1H, d, J=7.6 Hz), 7.7–7.9 (3H, m), 8.05 (1H, d, J=9.1 Hz), 8.15 (1H, d, J=7.6 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1279 (M^++Na)

Elemental Analysis Calcd. for $C_{54}H_{73}N_8O_{23}SNa.5H_2O$: C 48.14, H 6.21, H 8.32 Found: C 48.43, H 6.28, N 8.30

EXAMPLE 9

IR (KRr): 3347, 2956, 1664, 1633, 1508, 1444, 1268, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.1 (9H, m), 1.06 (3H, d, J=5.9 Hz), 1.3–1.5 (8H, m), 1.6–2.0 (7H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.6–4.4 (17H, m), 4.7–5.0 (8H, m), 5.09 (1H, d, J=5.5 Hz), 5.16 (1H, d, J=3.1 Hz), 5.24 (1H, d, J=4.5 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (2H, m), 6.98 (1H, d, J=8.3 Hz), 7.05 (1H, d, J=1.7 Hz), 7.3–7.6 (5H, m), 8.08 (1H, d, J=8.9 Hz), 8.25 (1H, d, J=8.4 Hz), 8.54 (1H, d, J=7.5 Hz), 8.93 (1H, s)

FAB-MASS: m/z=1257 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{75}N_8O_{23}SNa.4H_2O$: C 47.78, H 6.40, H 8.57 Found: C 47.88, H 6.71, N 8.53

EXAMPLE 10

IR (KRr): 3350, 2931, 1664, 1625, 1529, 1440, 1276, 1226, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 0.97 (3H, d, J=6.7 Hz), 1.12 (3H, d, J=5.9 Hz), 1.2–1.5 (10H, m), 1.6–2.1 (5H, m), 2.1–2.4 (4H, m), 3.1–3.3 (1H, m), 3.5–4.6 (15H, m), 4.7–5.0 (3H, m), 5.0–5.2 (7H, m), 5.27 (1H, d, J=4.4 Hz), 5.55 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (2H, m), 7.0–7.2 (4H, m), 7.3–7.6 (2H, m), 7.90 (1H, d, J=8.8 Hz), 8.0–8.2 (2H, m), 8.8–8.9 (2H, m), 9.06 (1H, d, J=7.2 Hz)

FAB-MASS: m/z=1281 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{71}N_8O_{24}SNa.5H_2O$: C 47.18, H 6.05, H 8.30 Found: C 46.97, H 6.27, N 8.22

EXAMPLE 11

NMR (DMSO-D_6, δ): 0.87–1.05 (6H, m), 1.10 (3H, d, J=5.7 Hz), 1.3–1.5 (4H, m), 1.6–1.9 (5H, m), 2.2–2.5 (3H, m), 2.6 (1H, m), 3.1–3.2 (1H, m), 3.7–4.5 (15H, m), 4.8–5.1 (8H, m), 5.09 (1H, d, J=5.64 Hz), 5.16 (1H, d, J=3.2 Hz), 5.26 (1H, d, J=4.2 Hz), 5.52 (1H, d, J=6.0 Hz), 6.73 (2H, d, J=8.4 Hz), 6.8–6.9 (2H, m), 7.0–7.1 (3H, m), 7.2–7.4 (4H, m), 7.6–7.8 (6H, m), 8.11 (1H, d, J=8.4 Hz), 8.29 (1H, d, J=8.4 Hz), 8.51 (1H, d, J=7.7 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1273 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{22}SNa.4H_2O$: C 49.92, H 6.02, H 8.47 Found: C 49.79, H 6.14, N 8.45

EXAMPLE 12

IR (KRr): 3330, 2929, 1670, 1629, 1533, 1440, 1280, 1226, 1045, 804 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.2–1.6 (10H, m), 1.6–2.0 (5H, m), 2.1–2.5 (4H, m), 3.1–3.3 (1H, m), 3.6–4.5 (15H, m), 4.8 (9H , m), 5.17 (1H, d, J=3.0 Hz), 5.25 (1H, d, J=4.5 Hz), 5.56 (1H, d, J=5.6 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=6.8 Hz), 7.1–7.2 (3H, m), 7.3–7.5 (3H, m), 7.85 (1H , d, J=8.8 Hz), 8.0–8.2 (3H, m), 8.84 (1H, s), 8.96 (1H, d, J=7.2 Hz)

FAB-MASS: m/z=1269 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{71}N_8O_{22}S_2Na.4H_2O$: C 47.34, H 6.04, H 8.49 Found: C 47.21, H 5.96, N 8.41

EXAMPLE 13

IR (KRr): 3345, 2927, 1664, 1629, 1515, 1442, 1274, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.10 (3H, d, J=5.9 Hz), 1.2–1.4 (10H, m), 1.5–2.5

(8H, m), 2.46 (3H, s), 2.69 (2H, t, J=7.7 Hz), 3.1–3.4 (2H, m), 3.6–4.5 (17H, m), 4.8–5.2 (8H, m), 6.7–7.0 (3H, m), 7.05 (1H, d, J=1.7 Hz), 7.14 (1H, s), 7.3–7.6 (5H, m), 8.0–8.2 (2H, s), 8.47 (1H, d, J=7.0 Hz), 8.84 (1H , s)

FAB-MASS: m/z=1251 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{73}N_8O_{22}SNa.3H_2O$: C 49.61, H 6.21, H 8.73 Found: C 49.88, H 6.44, N 8.74

EXAMPLE 14

IR (KRr): 3340, 1672, 1627, 1542, 1513, 1440, 1268, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.7 Hz), 0.94 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=6.0 Hz), 1.2–1.4 (12H, m), 1.6–2.0 (5H, m), 2.1–2.4 (3H, m), 2.6 (1H, m), 2.96 (2H, t, J=7.4 Hz), 3.1–3.3 (1H, m), 3.6–4.5 (13H, m), 4.7–5.2 (11H, m), 5.50 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (2H, m), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.72 (1H, d, J=8.5 Hz), 7.91 (1H, d, J=8.4 Hz), 8.05 (1H, d, J=8.4 Hz), 8.2–8.4 (1H, m), 8.80 (1H, d, J=7.7 Hz), 8.83 (1H, s)

FAB-MASS: m/z=1252 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{72}N_9O_{22}SNa.6H_2O$: C 46.67, H 6.33, H 9.42 Found: C 46.72, H 6.53, N 9.45

EXAMPLE 15

IR (KRr): 3350, 2935, 1664, 1627, 1517, 1446, 1251, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.90–1.1 (6H, m), 1.10 (3H, d, J=5.9 Hz), 1.2–1.4 (6H, m), 1.6–2.4 (8H, m), 2.6–2.7 (1H, m), 3.1–3.3 (1H, m), 3.7–4.5 (16H, m), 4.7–5.4 (11H, m), 5.51 (1H, d, J=5.6 Hz), 6.7–7.0 (3H, m), 7.0–7.6 (7H , m), 7.74 (1H, d, J=8.6 Hz), 8.0–8.4 (5H , m), 8.7–8.8 (1H , m), 8.84 (1H, s)

FAB-MASS: m/z=1301 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{71}N_{10}O_{22}SNa.6H_2O$: C 47.62, H 6.03, H 10.01 Found: C 47.65, H 6.03, N 10.03

EXAMPLE 16

IR (KRr): 3353, 1668, 1627, 1540, 1515, 1500 cm^{-1}

NMR (DMSO-d_6, δ): 0.80–1.00 (6H, m), 1.06 (3H, d, J=5.9 Hz), 1.20–1.53 (4H, m), 1.60–1.95 (5H, m), 2.00–2.65 (8H, m), 2.80 (2H, t, J=7.5 Hz), 3.05–3.45 (1H, m), 3.50–3.85 (2H, m), 3.90–4.48 (11H, m), 4.65–5.38 (11H, m), 5.47 (1H, d, J=6.0 Hz), 6.65–6.90 (2H, m), 6.90–7.10 (2H, m), 7.10–7.65 (11H, m), 7.90–8.25 (2H, m), 8.30 (1H, d, J=7.8 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1275.3 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{22}SNa.3H_2O$: C 50.53, H 6.09, H 8.57 Found: C 50.48, H 6.39, N 8.57

EXAMPLE 17

IR (Nujol): 3351, 1656, 1623, 1538, 1515 cm^{-1}

NMR (DMSO-D_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.8 Hz), 1.15–1.40 (8H, m), 1.50–2.00 (5H, m), 2.10–2.48 (4H, m), 2.52–2.70 (2H, m), 3.05–3.28 (1H, m), 3.60–4.50 (13H, m), 4.70–5.20 (9H, m), 5.25 (1H, d, J=4.6 Hz), 5.52 (1H, d, J=6.0 Hz), 6.68–6.92 (4H, m), 7.04 (1H, d, J=1.0 Hz), 7.22–7.50 (5H, m), 7.55–7.82 (7H, m), 8.14 (1H, d, J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz), 8.54 (1H, d, J=7.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1285 (M^++Na)

EXAMPLE 18

IR (Nujol): 3351, 1668, 1627, 1540, 1515 cm^{-1}

NMR (DMSO-D_6, δ): 0.87 (3H, t, J=6.8 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.8 Hz), 1.17–1.48 (4H, m), 1.50–1.95 (5H, m), 2.05–2.70 (8H, m), 2.70–2.95 (2H, m), 3.05–3.30 (1H, m), 3.60–3.90 (2H, m), 3.90–4.50 (11H, m), 4.65–5.10 (9H, m), 5.15 (1H, d, J=3.2 Hz), 5.23 (1, d, J=4.2 Hz), 5.48 (1H, d, J=6.0 Hz), 6.67–6.90 (3H, m), 7.03 (1H, d, J=1.5 Hz), 7.15–7.80 (11H, m), 8.00–8.20 (2H, m), 8.29 (1H, d, J=7.8 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1259 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{21}SNa.6H_2O$: C 50.30, H 6.52, H 8.53 Found: C 50.42, H 6.50, N 8.45

EXAMPLE 19

IR (Nujol): 3351, 1668, 1652, 1623, 1540 cm^{-1}

NMR (DMSO-D_6, δ): 0.87 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=6.0 Hz), 1.25–1.45 (4H, m), 1.50–2.00 (5H, m), 2.05–2.48 (4H, m), 2.40–2.75 (2H, m), 3.60–4.50 (13H, m), 4.68–5.25 (10H, m), 5.27 (1H, d, J=4.5 Hz), 5.53 (1H, d, J=6.0 Hz), 6.67–6.98 (4H, m), 7.05 (1H, d, J=1.0 Hz), 7.22–7.58 (5H, m), 7.58–7.90 (7H, m), 8.16 (1H, d, J=9.0 Hz), 8.34 (1H, d, J=8.4 Hz), 8.57 (1H, d, J=7.7 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1258 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{21}SNa.5H_2O$: C 49.84, H 6.15, H 8.45 Found: C 49.77, H 6.27, N 8.39

EXAMPLE 20

IR (Nujol): 3353, 1670, 1629, 1540, 1508 cm^{-1}

NMR (DMSO-D_6, δ): 0.88 (3H, t, J=6.5 Hz), 0.97 (3H, d, J=6.8 Hz), 1.04 (3H, d, J=5.9 Hz), 1.20–1.58 (8H, m), 1.60–1.96 (5H, m), 2.08–2.60 (6H, m), 2.70–3.00 (2H, m), 3.00–3.40 (1H, m), 3.60–3.85 (2H, m), 3.85–4.50 (13H, m), 4.50–5.60 (12H, m), 6.65–6.90 (3H, m), 7.00–7.15 (3H, m), 7.18–7.50 (4H, m), 7.59 (1H, s), 7.62–7.78 (2H, m), 7.95–8.20 (2H, m), 8.30 (1H, d, J=7.7 Hz), 8.83 (1H, s)

FAB-MASS: m/z=1277 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{75}N_8O_{22}SNa.4H_2O$: C 49.77, H 6.30, H 8.44 Found: C 49.67, H 6.31, N 8.40

EXAMPLE 21

IR (Nujol): 3351, 1654, 1623, 1538, 1515 cm^{-1}

NMR (DMSO-D_6, δ): 0.87 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.20–1.58 (8H, m), 1.66–1.95 (5H, m), 2.10–2.60 (4H, m), 3.09–3.30 (1H, m), 3.58–4.60 (15H, m), 4.69–5.20 (10H, m), 5.24 (1H, d, J=4.5 Hz), 5.51 (1H, d, J=6.0 Hz), 6.68–6.95 (4H, m), 7.04 (1H, d, J=1.0 Hz), 7.10–7.73 (7H, m), 7.73–7.90 (2H, m), 7.98 (1H, d, J=1.9 Hz), 8.10 (1H, d, J=8.4 Hz), 8.32 (1H, d, J=8.4 Hz), 8.50 (1H, d, J=7.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1275 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{22}SNa.5H_2O$: C 50.38, H 6.38, H 8.55 Found: C 49.98, H 6.37, N 8.41

EXAMPLE 22

IR (Nujol): 3340, 2931, 1664, 1627, 1531, 1444, 1278, 1047 cm^{-1}

NMR (DMSO-D_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.96 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=5.9 Hz), 1.2–1.4 (6H, m), 1.5–1.7 (2H, m), 1.7–2.1 (3H, m), 2.2–2.4 (3H, m), 2.6–2.7 (3H, m), 3.1–3.2 (1H, m), 3.7–4.6 (13H, m), 4.78 (1H, d, J=6.0 Hz),

4.8–5.1 (1H, m), 5.09 (1H, d, J=5.6 Hz), 5.16 (1H, d, J=3.2 Hz), 5.24 (1H, d, J=4.4 Hz), 5.52 (1H, d, J=6.0 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (2H, d, J=8.3 Hz), 7.05 (1H, s), 7.3–7.5 (5H, m), 7.65 (2H, d, J=8.2 Hz), 7.74 (2H, d, J=8.4 Hz), 7.98 (2H, d, J=8.4 Hz), 8.11 (1H, d, J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz), 8.79 (1H, d, J=7.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1245 (M^++Na)

Elemental Analysis Calcd. for $C_{54}H_{71}N_8O_{21}SNa.4H_2O$: C 50.07, H 6.15, H 8.65 Found: C 50.26, H 6.44, N 8.67

EXAMPLE 23

NMR (DMSO-D_6, δ): 0.91 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.8 Hz), 1.05 (3H, d, J=5.6 Hz), 1.2–1.5 (6H, m), 1.6–2.1 (5H, m), 2.1–2.7 (5H, m), 3.0–3.5 (9H, m), 3.6–4.5 (15H, m), 4.6–5.6 (11H, m), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (4H, m), 6.95 (2H, d, J=8.6 Hz), 7.02 (2H, d, J=9.2 Hz), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.82 (2H, d, J=8.6 Hz), 8.06 (1H, d, J=8 Hz), 8.25 (1H, d, J=6.7 Hz), 8.43 (1H, d, J=6.7 Hz), 8.85 (1H, s)

IR (KBr): 3350, 1668, 1629, 1510 cm^{-1}

FAB-MASS: m/z=1345 (M+Na)

Elemental Analysis Calcd. for $C_{58}H_{79}N_{10}O_{22}SNa.6H_2O$: C 48.67, H 6.41, N 9.78 Found: C 48.80, H 6.46, N 9.82

EXAMPLE 24

Major product

IR (KBr): 3350, 1668, 1631, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.7 Hz), 1.2–1.6 (10H, m), 1.6–2.4 (8H, m), 2.5–2.7 (1H, m), 3.18 (1H, m), 3.21 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.6–3.83 (2H, m), 3.83–4.6 (13H, m), 4.7–5.4 (11H, m), 5.51 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.2 Hz), 6.85 (1H, s), 7.04 (2H, d, J=8.4 Hz), 7.06 (1H, s), 7.31 (1H, s), 7.2–7.5 (2H, m), 7.67 (2H, d, J=8.4 Hz), 7.71 (2H, d, J=8.4 Hz), 7.96 (2H, d, J=8.4 Hz), 8.06 (1H, d, J=8 Hz), 8.25 (1H, d, J=6.7 Hz), 8.74 (1H, d, J=6.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1319 (M+Na)

Elemental Analysis Calcd. for $C_{57}H_{77}N_8O_{23}SNa.4H_2O$: C 49.99, H 6.26, N 8.18 Found: C 49.74, H 6.27, N 8.06

Minor Product

IR (KBr): 3350, 1668, 1631 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.7 Hz), 1.2–1.6 (6H, m), 1.6–2.1 (7H, m), 2.1–2.5 (3H, m), 2.5–2.7 (1H, m), 3.18 (1H, m), 3.6–3.8 (2H, m), 3.8–4.6 (13H, m), 4.6–5.2 (12H, m), 5.26 (1H, d, J=4.6 Hz), 5.53 (1H, d, J=5.8 Hz), 5.6–6.0 (1H, m), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.3 Hz), 6.85 (1H, s), 7.04 (2H, d, J=8.5 Hz), 7.06 (1H, s), 7.30 (1H, s), 7.2–7.5 (2H, m), 7.68 (2H, d, J=8.5 Hz), 7.72 (2H, d, J=8.5 Hz), 7.96 (2H, d, J=8.5 Hz), 8.06 (1H, d, J=8 Hz), 8.25 (1H, d, J=6.7 Hz), 8.74 (1H, d, J=6.7 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1287 (M+Na)

Elemental Analysis Calcd. for $C_{56}H_{73}N_8NaO_{22}S.7H_2O$: C 48.34, H 6.30, H 8.05 Found: C 48.19, H 6.19, N 7.99

EXAMPLE 25

IR (KRr): 3350, 2935, 2873, 1668, 1629, 1538, 1506, 1437, 1257, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.0 (6H, m), 1.08 (3H, d, J=5.7 Hz), 1.2–1.6 (4H, m), 1.6–2.0 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.6–4.6 (15H, m), 4.7–5.2 (10H, m), 5.26 (1H, d J=4.5 Hz), 5.55 (1H, d, J=5.9 Hz), 6.7–6.9 (3H, m), 7.0–7.6 (7H, m), 7.85 (2H, d, J=8.6 Hz), 7.9–8.2 (4H, m), 8.26 (1H, d, J=7.7 Hz), 8.8–9.0 (2H, m)

FAB-MASS: m/z=1314.3 ($M+Na)^+$

Elemental Analysis Calcd. for $C_{56}H_{70}N_9O_{23}NaS.7H_2O$: C 47.42, H 5.97, H 8.89 Found: C 47.33, H 5.85, N 8.73

EXAMPLE 26

To a solution of The Starting Compound (1 g) and succinimido 4-(4-octyloxyphenyl)piperazine-1-carboxylate (0.45 g) in N,N-dimethylformamide (10 mL) was added 4-dimethylaminopyridine (0.141 g), and stirred for 5 days at 50° C. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel.ODS-AM.S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give crude The Object Compound (23). The powder of crude The Object Compound (23) was purified by preparative HPLC utilizing a C_{18} μ Bondapak resin (Waters Associates, Inc.) which was eluted with a solvent system comprised of (acetonitrile-pH 3 phosphate buffer=40:60) at a flow rate of 80 ml/minute using a Shimadzu LC-8A pump. The column was monitored by a UV detector set at 240 um. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel.ODS-AM.S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (23) (60 mg).

IR (KBr): 3347, 1629, 1511, 1245 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.95 (3H, d, J=6.8 Hz), 1.06 (3H, d, J=5.9 Hz), 1.2–1.5 (10H, m), 1.55–1.92 (5H, m), 2.0–2.65 (4H, m), 2.8–3.05 (5H, m), 3.2–4.47 (17H, m), 4.6–5.6 (12H, m), 6.6–7.0 (7H, m), 7.03 (1H, s), 7.2–7.5 (3H, m), 7.9–8.3 (3H, m), 8.94 (1H, s)

FAB-MASS: m/z=1297 (M^++Na)

Elemental Analysis Calcd. for $C_{54}H_{79}N_{10}O_{22}SNa.6H_2O.CH_3CN$: C 47.22, H 6.65, H 10.82 Found: C 47.58, H 7.05, N 10.85

EXAMPLE 27

To a suspension of 1-hydroxybenzotriazole (0.53 g) and 2-(4-octyloxyphenoxy)acetic acid (1 g) in dichloromethane (30 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (WSCD.HCl) (0.886 g), and stirred for 3 hours at ambient temperature. The reaction mixture was added to water. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-[2-(4-octyloxyphenoxy)acetyl]benzotriazole 3-oxide (892 mg). To a solution of The Starting Compound (1.79 g) and 1-[2-(4-octyloxyphenoxy]benzotriazole 3-oxide (892 mg) in N,N-dimethylformamide (18 ml) was added 4-(N, N-dimethylamino)pyridine (0.297 g), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected

by filtration, and dried under reduced pressure. The powder was added to water, and subjected to ion-exchange column chromatography on DOWEX-50WX4, and eluted with water. The fractions containing the object compound were combined, and subjected to column chromatograph on ODS (YMC-gel.ODS-AM.S-50), and eluted with 50% methanol aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give The Object Compound (24) (1.75 g).

IR (KBr): 3350, 1666, 1629, 1228 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.9 Hz), 0.95 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.7 Hz), 1.15–1.5 (10H, m), 1.55–2.0 (5H, m), 2.05–2.5 (4H, m), 3.16 (1H, m), 3.72 (2H, m), 3.88 (3H, t, J=6.3 Hz), 4.41 (2H, s), 3.93–4.6 (11H, m), 4.69–5.25 (10H, m), 5.28 (1H, d, J=4.3 Hz), 5.57 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (5H, m), 7.04 (1H, s), 7.09 (1H, s), 7.3–7.4 (2H, m), 7.92–8.17 (2H, m), 8.29 (1H, d, J=7.5 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1243 (M^++Na)

Elemental Analysis Calcd. for $C_{51}H_{73}N_8O_{23}SNa.4H_2O$: C 47.36, H 6.31, H 8.66 Found: C 47.22, H 6.44, N 8.37

The Object Compounds (28) to (31) were obtained according to a similar manner to that of Example 27.

EXAMPLE 28

IR (KBr): 3350, 2933, 1664, 1628, 1446, 1205, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.81–1.1 (9H, m), 1.2–2.0 (19H, m), 2.1–2.3 (3H, m), 3.6–3.8 (4H, m), 3.9–4.4 (13H, m), 4.6–5.0 (8H, m), 5.07 (1H, d, J=5.6 Hz), 5.14 (1H, d, J=3.2 Hz), 5.23 (1H, d, J=4.3 Hz), 5.46 (1H, d, J=6.7 Hz), 6.7–6.9 (3H, m), 7.04 (1H, s), 7.2–7.5 (6H, m), 7.8–8.0 (3H, m), 8.05 (1H, d, J=8.4 Hz), 8.2–8.4 (2H, m), 8.83 (1H, s)

FAB-MASS: m/z=1360 (M^++Na)

Elemental Analysis Calcd. for $C_{59}H_{80}N_9O_{23}SNa.4H_2O$: C 48.99, H 6.41, H 8.72 Found: C 48.92, H 6.37, N 8.64

EXAMPLE 29

IR (KBr): 3350, 2927, 1668, 1627, 1535, 1515, 1452, 1440, 1286, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.83 (3H, t, J=6.7 Hz), 0.95 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.9 Hz), 1.2–1.4 (12H, m), 1.6–2.0 (5H, m), 2.1–2.4 (3H, m), 2.6 (1H, m), 2.82 (2H, t, J=7.4 Hz), 3.1–3.2 (1H, m), 3.6–4.5 (13H, m), 4.7–5.2 (11H, m), 5.4–5.6 (1H, m), 6.72 (1H, d, J=8.2 Hz), 6.82 (2H, d, J=8.1 Hz), 7.03 (1H, s), 7.2–7.4 (3H, m), 7.47 (1H, d, J=8.5 Hz), 7.69 (1H, d, J=8.5 Hz), 8.1–8.2 (2H, m), 8.23 (1H, d, J=8.4 Hz), 8.62 (1H, d, J=7.8 Hz), 8.83 (1H, s)

FAB-MASS: m/z=1251 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{73}N_{10}O_{21}SNa.5H_2O$: C 47.34, H 6.34, H 10.61 Found: C 47.30, H 6.45, N 10.45

EXAMPLE 30

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 0.96 (3H, d, J=6.7 Hz), 1.05 (3H, d, J=5.8 Hz), 1.2–1.5 (10H, m), 1.6–2.0 (5H, m), 2.2–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.7–4.5 (15H, m), 4.7–5.0 (8H, m), 5.10 (1H, d, J=5.6 Hz), 5.17 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.5 Hz), 5.52 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (3H, m), 7.04 (1H, s), 7.2–7.4 (3H, m), 8.0–8.3 (3H, m), 8.68 (1H, d, J=2.3 Hz), 8.7–8.8 (1H, m), 8.85 (1H, m)

FAB-MASS: m/z=1214 (M^++Na)

Elemental Analysis Calcd. for $C_{49}H_{70}N_9O_{22}SNa.4H_2O$: C 46.55, H 6.22, H 9.97 Found: C 46.29, H 6.18, N 9.71

EXAMPLE 31

IR (Nujol): 3342, 2210, 1668, 1623 cm^{-1}

NMR (DMSO-D_6, δ): 0.88 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=6.7 Hz), 1.20–1.60 (8H, m), 1.60–2.00 (5H, m), 2.05–2.50 (4H, m), 3.05–3.30 (1H, m), 3.60–4.60 (15H, m), 4.65–5.18 (10H, m), 5.24 (1H, d, J=4.5 Hz), 5.58 (1H, d, J=6.0 Hz), 6.68–7.10 (4H, m), 7.15–7.65 (5H, m), 7.80–8.30 (6H, m), 8.84 (1H, s), 9.18 (1H, d, J=7.7 Hz)

FAB-MASS: m/z=1273.5 (M^++Na)

EXAMPLE 32

To a solution of 6-heptyloxy-2-naphthoic acid (0.358 g) and triethylamine (0.174 ml) in N,N-dimethylformamide (10 ml) was added diphenylphophoryl azide (0.4 ml), and stirred for an hour at ambient temperature. Then, the reaction mixture was stirred for an hour at 100° C. After cooling, to the reaction mixture was added The Starting Compound (1 g) and 4-(N,N-dimethylamino)pyridine (0.140 g), and stirred for 10 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel.ODS-AM.S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (29) (0.832 g).

IR (KRr): 3350, 1664, 1629, 1546, 1240 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.2–1.55 (8H, m), 1.55–2.0 (5H, m), 2.1–2.5 (4H, m), 3.18 (1H, m), 3.6–3.8 (3H, m), 3.9–4.5 (13H, m), 4.7–4.95 (3H, m), 5.0–5.3 (7H, m), 5.59 (1H, d, J=5.8 Hz), 6.52 (1H, d, J=8.1 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.2 Hz), 6.90 (1H, s), 7.0–7.15 (3H, m), 7.20 (1H, s), 7.27–7.4 (3H, m), 7.6–7.7 (2H, m), 7.87 (1, s), 7.95–8.2 (2H, m), 8.69 (1H, s), 8.85 (1H, s)

FAB-MASS: m/z=1264 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{72}N_9O_{22}SNa.5H_2O$: C 47.78, H 6.20, H 9.46 Found: C 47.65, H 6.42, N 9.34

The Object Compound (33) was obtained according to a similar manner to that of Example 32.

EXAMPLE 33

IR (KRr): 3350, 1666, 1629, 1537, 1240 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.8 Hz), 1.2–1.55 (8H, m), 1.55–2.0 (5H, m), 2.07–2.6 (4H, m), 3.18 (1H, m), 3.6–3.85 (3H, m), 3.9–4.5 (13H, m), 4.7–4.98 (3H, m), 5.0–5.3 (7H, m), 5.57 (1H, d, J=5.9 Hz), 6.50 (1H, d, J=8.1 Hz), 6.73 (1H, d, J=8.2 Hz), 6.82 (1H, dd, J=8.2 and 1.7 Hz), 6.87 (1H, s), 6.97 (2H, d, J=8.8 Hz), 7.05 (1H, d, J=1.7 Hz), 7.10 (1H, s), 7.23–7.43 (2H, m), 7.38 (2H, d, J=8.8 Hz), 7.50 (2H, d, J=8.8 Hz), 7.52 (2H, d, J=8.8 Hz), 8.0–8.15 (2H, m), 8.65 (1H, s), 8.84 (1H, s)

FAB-MASS: m/z=1290 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{74}N_9O_{22}SNa.7H_2O$: C 47.38, H 6.36, H 9.04 Found: C 47.67, H 6.53, N 9.03

EXAMPLE 34

A solution of The Starting Compound (2.45 g), 3-[4-(4-pentylphenyl)phenyl]propiolic acid (0.90 g), 1-ethyl-3-(3'-

dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl) (0.59 g) and triethylamine (0.43 ml) in N,N-dimethylformamide (50 ml) was stirred for 15 hours at ambient temperature. The reaction mixture was diluted with ethyl acetate, and the resultant precipitate was collected by filtration, and washed in turn with ethyl acetate and diisopropyl ether, and dried under reduced pressure. The powder was dissolved in water, and was subjected to column chromatography on ion exchange resin (DOWEX-50WX4 (Na form, 50 ml)) eluting with water. The fractions containing the object compound were combined, and subjected to reversed phase chromatography on ODS (YMC-gel.ODS-AM.S-50, 50 ml) eluting with (water:acetonitrile=10:0–7:3, V/V. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (31) (1.53 g).

IR (KRr): 3351, 2212, 1668, 1627 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.8 Hz), 1.20–1.50 (4H, m), 1.50–2.00 (5H, m), 2.03–2.55 (4H, m), 2.62 (2H, t, J=7.5 Hz), 3.17 (1H, t, J=8.4 Hz), 3.55–4.57 (15H, m), 4.65–5.13 (9H, m), 5.16 (1H, d, J=3.2 Hz), 5.24 (1H, d, J=4.5 Hz), 5.58 (1H, d, J=5.8 Hz), 6.67–6.90 (3H, m), 6.93–7.10 (2H, m), 7.15–7.50 (4H, m), 7.50–7.90 (6H, m), 8.06 (1H, d, J=8.4 Hz), 8.15 (1H, d, J=7.7 Hz), 8.84 (1H, s), 9.19 (1H, d, J=7.1 Hz)

FAB-MASS: m/z=1255 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{69}N_8O_{21}SNa.4H_2O$: C 50.61, H 5.95, H 8.58 Found: C 50.47, H 6.00, N 8.54

EXAMPLE 35

To a suspension of 1-hydroxybenzotriazole (501 mg) and 4-(4-heptylphenyl)benzoic acid (1 g) in dichloromethane (30 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (WSCD.HCl) (839 mg), and stirred for 3 hours at ambient temperature. The reaction mixture was added to water. The organic layer was separated, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-[4-(4-heptylphenyl) benzoyl]benzotriazole 3-oxide. To a solution of The Starting Compound (2.49 g) and 1-[4-(4-heptylphenyl)benzoyl] benzotriazole 3-oxide in N,N-dimethylformamide (25 ml) was added 4-(N,N-dimethylamino)pyridine (381 mg), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The residue was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-5WX4) eluting with water. The fraction containing the object compound were combined, and subjected to column chromatography on ODSD (YMC-gel.ODS-AM.S-50) eluting with 30% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (32) (1.99 g).

IR (Nujol): 3350, 2852, 1749, 1621, 1457, 1376, 1045 cm^{-1}

NMR (DMSO-D_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.5–1.7 (2H, m), 1.7–2.2 (3H, m), 2.2–2.5 (3H, m), 2.6–2.8 (3H, m), 3.1–3.2 (1H, m), 3.7–4.6 (13H, m), 4.7–5.2 (8H, m), 5.12 (1H, d, J=5.5 Hz), 5.18 (1H, d, J=2.9 Hz), 5.27 (1H, d, J=4.4 Hz), 5.54 (1H, d, J=5.8 Hz), 6.7–6.9 (3H, m), 7.05 (1H, s), 7.2–7.4 (5H, m), 7.65 (2H, d, J=8.0 Hz), 7.74 (2H, d, J =8.3 Hz), 7.98 (2H, d, J=8.3 Hz), 8.11 (1H, d, J=8.7 Hz), 8.28 (1H, d, J=8.4 Hz), 8.78 (1H, d, J=7.3 Hz), 8.95 (1H, s)

FAB-MASS: m/z=1259 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{21}SNa.5H_2O$: C 49.77, H 6.30, H 8.44 Found: C 49.98, H 6.44, N 8.41

The Object Compounds (36) to (107) were obtained according to a similar manner to that of Example 1.

EXAMPLE 36

IR (KRr): 3350, 1675.8, 1629.6, 1515.8 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (6H, t, J=6.6 Hz), 0.96 (3H, d, J=6.6 Hz), 1.06 (3H, d, J=5.7 Hz), 1.1–1.3 (2H, m), 1.4–2.0 (6H, m), 2.0–2.7 (4H, m), 3.1–3.5 (9H, m), 3.66 (2H, t, J=7.3 Hz), 3.6–4.5 (13H, m), 4.7–5.6 (12H, m), 6.73 (1H, d, J=8.3 Hz), 6.82 (1H, d, J=8.3 Hz), 6.8–6.9 (1H, m), 7.02 (2H, d, J=9.0 Hz), 7.04 (1H, s), 7.11 (2H, d, J=9.0 Hz), 7.2–7.6 (3H, m), (7.50 (2H, d, J=9.0 Hz), 7.82 (2H, d, J=9.0 Hz), 8.1 (1H, d, J=8.5 Hz), 8.28 (1H, d, J=8.5 Hz), 8.33 (1H, s), 8.45 (1H, d, J=7.0 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1412 (M+Na)

Elemental Analysis Calcd. for $C_{60}H_{80}N_{13}O_{22}SNa.9H_2O$: C 46.42, H 6.36, H 11.73 Found: C 46.64, H 6.43, N 11.62

EXAMPLE 37

IR (KRr): 3350, 1668.1, 1629.6, 1268.9 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.6 Hz), 0.96 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.9 Hz), 1.2–1.4 (10H, m), 1.4–2.0 (5H, m), 2.0–2.5 (4H, m), 2.61 (2H, t, J=7.2 Hz), 3.1–3.3 (1H, m), 3.6–4.5 (13H, m), 4.40 (2H, s), 4.6–5.3 (11H, m), 5.60 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.82 (1H, d, J=8.2 Hz), 6.6–6.9 (1H, m), 7.04 (1H, s), 7.0–7.1 (1H, m), 7.32 (2H, d, J=8.5 Hz), 7.2–7.5 (2H, m), 7.58 (2H, d, J=8.5 Hz), 7.93 (1H, d, J=7 Hz), 8.04 (1H, d, J=9.4 Hz), 8.41 (1H, s), 8.44 (1H, d, J=9.4 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1294 (M+Na)

Elemental Analysis Calcd. for $C_{53}H_{74}N_{11}O_{22}SNa.7H_2O$: C 45.52, H 6.34, H 11.02 Found: C 45.57, H 6.27, N 10.93

EXAMPLE 38

Major product

IR (KBr): 3349.7, 1670.1, 1627.6, 1508.1 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.06 (3H, d, J=5.7 Hz), 1.2–1.6 (8H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.0–3.2 (5H, m), 3.21 (3H, s), 3.30 (2H, t, J=6.5 Hz), 3.3–3.5 (4H, m), 3.6–4.5 (15H, m), 4.7–5.3 (11H, m), 5.49 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.3 Hz), 6.8–6.9 (4H, m), 6.95 (2H, d, J=9.2 Hz), 7.01 (2H, d, J=8.5 Hz), 7.04 (1H, s), 7.20 (1H, s), 7.2–7.5 (2H, m), 7.81 (2H, d, J=8.5 Hz), 8.09 (1H, d, J=8.7 Hz), 8.28 (1H, d, J=8.7 Hz), 8.45 (1H, d, J=6.7 Hz), 8.84 (1, s)

FAB-MASS: m/z=1389 (M+Na)

Elemental Analysis Calcd. for $C_{60}H_{83}N_{10}O_{23}SNa.8H_2O$: C 47.68, H 6.60, N 9.27 Found: C 49.83, H 6.72, N 9.27

Minor Product

IR (KBr): 3338.2, 1646.9, 1151.9 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.7 Hz), 1.3–1.6 (4H, m), 1.6–2.7 (11H, m), 3.0–3.2 (5H, m), 3.3–3.5 (4H, m), 3.6–4.5 (15H, m), 4.7–5.3 (13H, m), 5.48 (1H, d, J=5.9 Hz), 5.7–6.0 (1H, m), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (4H, m), 6.94 (2H, d, J=9.3 Hz),7.01 (2H, d, J=8.6 Hz), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.81 (2H, d, J=8.6 Hz), 8.06 (1H, d, J=8.7 Hz), 8.25 (1H, d, J=8.7 Hz), 8.42 (1H, d, J=6.7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1357 (M+Na) Elemental Analysis Calcd. for $C_{59}H_{79}N_{10}O_{22}SNa.9H_2O$: C, 47.32; H, 6.53; N, 9.35. Found: C, 47.08; H, 6.66; N,9.25.

EXAMPLE 39

IR (KBr): 3350, 1670.1, 1631.5, 1510.0, 1234.2 cm^{-1} NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.6 Hz), 1.2–1.5 (8H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.0–3.3 (5H, m), 3.3–3.5 (4H, m), 3.6–3.8 (2H, m), 3.88 (2H, d, J=6.4 Hz), 3.8–4.5 (11H, m), 4.7–5.1 (8H, m), 5.10 (1H, d, J=5.6 Hz), 5.16 (1H, d, J=3.1 Hz), 5.25 (1H, d, J=4.5 Hz), 5.48 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (4H, m), 6.94 (2H, d, J=9.3 Hz), 7.01 (2H, d, J=8.7 Hz), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.81 (2H, d, J=8.7 Hz), 8.06 (1H, d, J=8 Hz), 8.25 (1H, d, J=6.7 Hz), 8.43 (1H, d, J=6.7 Hz), 8.85 (1H, s) FAB-MASS: m/z=1359 (M+Na) Elemental Analysis Calcd. for $C_{59}H_{81}N_{10}O_{22}SNa.5H_2O$: C, 49.64; H, 6.43; N, 9.81. Found: C, 49.49; H, 6.54; N, 9.72.

EXAMPLE 40

IR (KBr): 3355.5, 1670.1, 1627.6, 1510.0 1236.1 cm^{-1} NMR (DMSO-d_6, δ): 0.89 (6H, d, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.05 (3H, d, J=7.5 Hz),1.2–1.4 (2H, m), 1.5–2.1 (6H, m), 2.1–2.7 (4H, m), 3.0–3.6 (9H, m), 3.6–4.5 (15H, m), 4.5–5.4 (12H, m), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (4H, m), 6.96 (2H, d, J=9.6 Hz), 7.02 (2H, d, J=8.7 Hz), 7.05 (1H, s), 7.2–7.5 (3H, m), 7.82 (2H, d, J=8.7 Hz), 8.08 (1H, d, J=8 Hz), 8.27 (1H, d, J=6.7 Hz), 8.46 (1H, d, J=6.7 Hz), 8.85 (1H, s) FAB-MASS: m/z=1345 (M+Na) Elemental Analysis Calcd. for $C_{58}H_{79}N_{10}O_{22}SNa.8H_2O$: C, 47.47; H, 6.52; N, 9.54. Found: C, 47.47, H, 6.54; N, 9.51.

EXAMPLE 41

IR (KBr): 3347.8, 1668.1, 1629.6, 1510.0, 1234.2 cm^{-1} NMR (DMSO-d_6, δ): 0.89 (3H, t, J=7.0 Hz), 0.96 (3H, d, J=6.7 Hz), 1.05 (3H, d, J=5.8 Hz), 1.2–1.5 (4H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.0–3.6 (9H, m), 3.6–3.8 (1H, m), 3.8–4.5 (13H, m), 4.7–5.6 (12H, m), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (4H, m), 6.96 (2H, d, J=8.7 Hz), 7.02 (2H, d, J=9.0 Hz), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.82 (2H, d, J=8.7 Hz), 8.07 (1H, d, J=8 Hz), 8.27 (1H, d, J=6.7 Hz), 8.45 (1H, d, J=6.7 Hz), 8.85 (1H, s) FAB-MASS: m/z=1331 (M+Na) Elemental Analysis Calcd. for $C_{57}H_{77}N_{10}O_{22}SNa.6H_2O$: C, 48.30; H, 6.33; N, 9.88. Found: C, 48.20; H, 6.58; N, 10.03.

EXAMPLE 42

Mixture product

IR (KBr): 3344, 1670.1, 1631.5 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.2–1.5 (8H, m), 1.6–2.1 (7H, m), 2.1–2.7 (4H, m), 3.1–3.3 (1H, m), 3.6–4.5 (15H, m), 4.45 and 4.70 (2H, t, J=7.1 Hz), 4.6–5.3 (11H, m), 5.52 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.2 Hz), 6.85 (1H, s), 7.03 (2H, d, J=8.6 Hz), 7.05 (1H, s), 7.2–7.5 (3H, m), 7.68 (2H, d, J=8.6 Hz), 7.71 (2H, d, J=8.4 Hz), 7.96 (2H, d, J=8.4 Hz), 8.12 (1H, d, J=8.5 Hz), 8.30 (1H, d, J=7.0 Hz) FAB-MASS: m/z=1357 (M+Na) Elemental Analysis Calcd. for $C_{57}H_{75}N_{12}O_{22}SNa.4H_2O$: C, 48.64; H, 5.94; N, 11.94. Found: C, 48.91; H, 5.88; N, 11.86.

EXAMPLE 43

IR (KBr): 3350, 1666.2, 1651.5 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.05 (6H, d, J=6.3 Hz), 1.06 (3H, d, J=5.7 Hz), 1.2–1.6 (10H, m), 1.6–2.1 (7H, m), 2.1–2.7 (6H, m), 2.8–3.0 (2H, m), 3.0–3.2 (1H, m), 3.4–3.7 (2H, m), 3.6–3.8 (2H, m), 3.8–4.5 (13H, m), 4.7–5.6 (12H, m), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (2H, m), 7.03 (2H, d, J=8.7 Hz), 7.06 (1H, s), 7.2–7.5 (3H, m), 7.67 (2H, d, J=8.7 Hz), 7.71 (2H, d, J=8.4 Hz), 7.96 (2H, d, J=8.4 Hz), 8.04 (1H, d, J=8.5 Hz), 8.31 (1H, d, J=8.5 Hz), 8.73 (1H, d, J=7.0 Hz), 8.90 (1H, s) FAB-MASS: m/z=1402 (M+Na)

EXAMPLE 44

IR (KBr pelet): 3350, 2929, 2856, 1670, 1631, 1510, 1243, 1045 cm^{-1} NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.7 Hz), 1.6–2.0 (5H, m), 2.2–2.5 (5H, m), 2.6–2.7 (1H, m), 3.0–3.3 (5H, m), 3.6–4.5 (19H, m) 4.77 (2H, d, J=5.9 Hz), 4.8–5.1 (6H, m), 5.10 (1H, d, J=5.6 Hz), 5.17 (1H, d, J=3.1 Hz), 5.25 (1H, d, J=4.5 Hz), 5.50 (1H, d, J=5.8 Hz), 6.7–7.0 (8H, m), 7.04 (1H, s), 7.2–7.4 (3H, m), 8.0–8.2 (2H, m), 8.26 (1H, d, J=8.0 Hz), 8.55 (1H, d, J=7.3 Hz), 8.67 (1H, d, J=1.2 Hz), 8.85 (1H, s) FAB-MASS: m/z=1374.3 ($M+Na^+$) Elemental Analysis Calcd. for $C_{59}H_{82}N_{11}O_{22}NaS.5.5H_2O$: C, 48.82; H, 6.46; N, 10.61. Found: C,48.89; H, 6.74; N, 10.50.

EXAMPLE 45

IR (KBr): 3350, 2935, 1668, 1623, 1538, 1257, 1174, 1047 cm^{-1} NMR (DMSO-d_6, δ): 0.8–1.1 (6H, m), 1.09 (3H, d, J=5.7 Hz), 1.2–1.6 (6H, m), 1.7–2.1 (5H, m), 2.2–2.4 (3H, m), 2.5–2.6 (1H, m), 3.6–3.8 (2H, m), 3.8–4.6 (14H, m), 4.8–5.2 (7H, m), 5.18 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.5 Hz), 5.54 (1H, d, J=5.8 Hz), 6.7–7.5 (9H, m), 7.82 (1H, d, J=8.5 Hz), 7.96 (1H, d, J=8.7 Hz), 8.1–8.4 (5H, m), 8.8–9.0 (2H, m) FAB-MASS: m/z=1302.6 ($M+Na^+$) Elemental Analysis Calcd. for $C_{55}H_{70}N_9O_{23}SNa.6H_2O$: C, 47.58; H, 5.95; N, 9.08. Found: C, 47.46; H, 6.04; N, 9.05.

EXAMPLE 46

IR (KBr): 3355, 2958, 1670, 1627, 1521, 1247, 1047 cm^{-1} NMR (DMSO-d_6, δ): 0.9–1.0 (6H, m), 1.08 (3H, d, J=5.6 Hz), 1.4–1.6 (2H, m), 1.7–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.7–3.8 (2H, m), 3.9–4.6 (13H, m), 4.8–5.1 (8H, m), 5.11 (1H, d, J=5.6 Hz), 5.17 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.5 Hz), 5.54 (1H, d, J=5.9 Hz), 6.7–6.9 (3H, m), 7.0–7.2 (3H, m), 7.3–7.5 (3H, m), 7.7–7.9 (8H, m), 8.02 (2H, d, J=8.4 Hz), 8.08 (1H, d, J=8.4 Hz), 8.32 (1H, d, J=7.7 Hz), 8.81 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1309.3 $(M+Na)^+$ Elemental Analysis Calcd. for $C_{58}H_{71}N_8O_{22}NaS.6H_2O$: C, 49.92; H, 6.00; N, 8.03. Found: C, 49.92; H, 5.97; N, 8.03.

EXAMPLE 47

IR (KBr): 3350, 2933, 1668, 1629, 1517, 1249, 1045 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.8 Hz), 1.7–2.7 (8H, m), 3.1–3.3 (1H, m), 3.6–4.5 (16H, m), 4.7–5.2 (8H, m), 5.18 (1H, d, J=3.1 Hz), 5.27 (1H, d, J=4.5 Hz), 5.56 (1H, d, J=5.8 Hz), 6.7–7.0 (3H, m), 7.0–7.2 (3H, m), 7.2–7.5 (3H, m), 8.0–8.4 (6H, m), 8.85 (1H, s), 8.96 (1H, d, J=7.0 Hz), 9.07 (1H, s) FAB-MASS: m/z=1276.6 ($M+Na^+$) Elemental Analysis Calcd. for $C_{54}H_{72}N_9O_{22}NaS.5H_2O$: C, 48.25; H, 6.15; N, 9.38. Found: C, 48.10; H, 6.14; N, 9.30.

EXAMPLE 48

IR (KBr): 3350, 2931, 1668, 1629, 1537, 1049 cm^{-1} NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.9 Hz), 0.9–1.5 (16H, m), 1.6–2.4 (8H, m), 2.5–2.7 (1H, m), 3.1–3.3 (1H, m), 3.5–5.6 (25H, m), 6.6–7.4 (8H, m), 7.8–8.4 (6H, m), 8.7–9.0 (2H, m), 9.00 (1H, d, J=2.4 Hz) FAB-MASS: m/z=1331.4 ($M+Na^+$) Elemental Analysis Calcd. for $C_{56}H_{73}N_{10}O_{23}NaS.8H_2O$: C, 46.28; H, 6.17; N, 9.64. Found: C, 46.50; H, 6.27; N, 9.65.

EXAMPLE 49

IR (KBr pelet): 3300, 2931, 1668, 1650, 1629, 1538, 1515, 1268, 1049 cm^{-1} NMR (DMSO-d_6, δ): 0.87 (3H, t,

J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.10 (3H, d, J=5.6 Hz), 1.2–1.4 (6H, m), 1.5–1.7 (2H, m), 1.7–2.1 (3H, m), 2.1–2.4 (3H, m), 2.6–2.7 (3H, m), 3.1–3.2 (1H, m), 3.7–3.9 (2H, m), 3.9–4.5 (12H, m), 4.8–5.1 (7H, m), 5.11 (1H, d, J=5.5 Hz), 5.18 (1H, d, J=3.1 Hz), 5.27 (1H, d, J=4.5 Hz), 5.55 (1H, d, J=5.8 Hz), 6.7–7.0 (3H, m), 7.06 (1H, s), 7.3–7.5 (5H, m), 7.72 (2H, d, J=8.2 Hz), 7.9–8.2 (5H, m), 8.3–8.4 (4H, m), 8.9–9.0 (2H, m) FAB-MASS: m/z=1260.5 ($M+Na^+$) Elemental Analysis Calcd. for $C_{61}H_{74}N_9O_{22}SNa.6H_2O$: C, 50.58; H, 5.98; N, 8.70. Found: C, 50.34; H, 6.16; N, 8.55.

EXAMPLE 50

IR (KBr): 3369, 2958, 2935, 1670, 1629, 1525, 1473, 1247, 1047 cm^{-1} NMR (DMSO-d_6, δ): 0.95 (3H, t, J=7.3 Hz), 0.97 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.7 Hz), 1.3–1.6 (2H, m), 1.7–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.7–4.6 (15H, m), 4.7–5.1 (8H, m), 5.10 (1H, d, J=5.6 Hz), 5.18 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.4 Hz), 5.56 (1H, d, J=5.7 Hz), 6.7–7.0 (3H, m), 7.1–7.2 (3H, m), 7.2–7.4 (3H, m), 7.70 (2H, d, J=8.6 Hz), 7.78 (2H, d, J=8.4 Hz), 8.1–8.4 (6H, m), 8.85 (1H, s), 8.99 (1H, d, J=7.0 Hz), 9.13 (1H, d, J=1.6 Hz) FAB-MASS: m/z=1310.1 $(M+Na)^+$ Elemental Analysis Calcd. for $C_{57}H_{70}N_9O_{22}NaS.7H_2O$: C, 47.20; H, 6.12; N, 8.69. Found: C, 47.42; H, 6.19; N, 8.92.

EXAMPLE 51

IR (KBr): 3351, 2937, 2875, 1670, 1627, 1533, 1245, 1047 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.7 Hz), 1.5–1.7 (2H, m), 1.7–2.1 (7H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.7–3.8 (2H, m), 3.9–4.6 (15H, m), 4.7–4.9 (3H, m), 5.0–5.1 (5H, m), 5.10 (1H, d, J=5.6 Hz), 5.17 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.5 Hz), 5.52 (1H, d, J=5.9 Hz), 6.7–7.1 (9H, m), 7.2–7.5 (5H, m), 7.68 (2H, d, J=8.2 Hz), 7.72 (2H, d, J=6.7 Hz), 7.96 (2H, d, J=8.2 Hz), 8.06 (1H, d, J=8.4 Hz), 8.28 (1H, d, J=7.7 Hz), 8.76 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1339.5 ($M+Na^+$) Elemental Analysis Calcd. for $C_{59}H_{73}N_8O_{23}NaS.7H_2O$: C, 49.09; H, 6.08; N, 7.76. Found: C, 49.04; H, 6.08; N, 7.82.

EXAMPLE 52

IR (KBr): 3350, 2954, 2937, 1670, 1631, 1440, 1257, 1047 cm^{-1} NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.8 Hz), 0.97 (3H, d, J=6.7 Hz), 1.09 (2H, d, J=5.8 Hz), 1.2–1.5 (6H, m), 1.7–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.7–4.6 (15H, m), 4.7–5.3 (11H, m), 5.5–5.6 (1H, m), 6.7–6.9 (1H, m), 7.0–7.5 (6H, m), 8.0–8.4 (8H, m), 8.85 (1H, s), 8.96 (1H, d, J=7.0 Hz) APCI-MASS: m/z=1329.0 $(M+Na)^+$ Elemental Analysis Calcd. for $C_{56}H_{71}N_{10}O_{23}NaS.6H_2O$: C, 47.52; H, 5.91; N, 9.90. Found: C, 47.42; H, 6.05; N, 9.90.

EXAMPLE 53

IR (KBr): 3350, 2952, 1666, 1629, 1537, 1519, 1255 cm^{-1} NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.4 Hz), 1.08 (3H, d, J=5.6 Hz), 1.7–2.4 (8H, m), 2.5–2.6 (1H, m), 3.7–4.5 (15H, m), 4.7–5.1 (8H, m), 5.11 (1H, d, J=5.5 Hz), 5.17 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=3.1 Hz), 5.56 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz), 6.7–7.0 (2H, m), 7.05 (1H, s), 7.13 (2H, d, J=8.7 Hz), 7.2–7.5 (3H, m), 7.97 (2H, d, J=8.7 Hz), 8.1–8.4 (6H, m), 8.85 (1H, s), 8.92 (1H, d, J=7.0 Hz) FAB-MASS: m/z=1345.3 $(M+Na)^+$ Elemental Analysis Calcd. for $C_{56}H_{71}N_{10}O_{22}S_2Na.8H_2O$: C, 45.84; H, 5.98, N, 9.55. Found: C, 45.87; H, 6.07; N, 9.55.

EXAMPLE 54

IR (KBr pelet): 3350, 2931, 1670, 1652, 1628, 1442, 1247, 1047 cm^{-1} NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.8 Hz), 1.12 (3H, d, J=6.8 Hz), 1.2–1.5 (10H, m), 1.7–2.0 (5H, m), 2.2–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.72 (2H, br), 3.8–4.5 (17H, m), 4.7–5.2 (9H, m), 5.26 (1H, d, J=4.6 Hz), 5.57 (1H, d, J=5.7 Hz), 6.7–7.1 (7H, m), 7.3–7.5 (3H, m), 7.66 (2H, d, J=8.7 Hz), 8.10 (1H, d, J=7.6 Hz), 8.17 (1H, d, J=7.6 Hz), 8.76 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1293 $(M+Na^+)$ Elemental Analysis Calcd. for $C_{54}H_{75}N_{10}O_{22}NaS.7H_2O$: C, 46.41; H, 6.42; N, 10.02. Found: C, 46.51; H, 6.43; N, 9.95.

EXAMPLE 55

IR (KBr): 3345, 2937, 1650, 1511, 1249, 1047, cm^{-1} NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.0 Hz), 0.96 (3H, t, J=7.8 Hz), 1.09 (3H, d, J=6.8 Hz), 1.3–1.5 (4H, m), 1.6–2.1 (5H, m), 2.1–2.5 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.7–3.9 (2H, m), 3.9–4.6 (13H, m), 4.79 (2H, d, J=5.9 Hz), 4.8–4.9 (1H, m), 4.9–5.2 (5H, m), 5.10 (1H, d, J=5.9 Hz), 5.17 (1H, d, J=3.1 Hz), 5.25 (1H, d, J=4.6 Hz), 5.53 (1H, d, J=5.9 Hz), 6.7–7.0 (3H, m), 7.0–7.2 (3H, m), 7.19 (1H, s), 7.3–7.5 (3H, m), 7.7–8.1 (6H, m), 8.08 (1H, d, J=10.0 Hz), 8.26 (1H, d, J=8.8 Hz), 8.77 (1H, m), 8.85 (1H, s), 13.32 (1H, s) FAB-MASS: m/z=1314.0 $(M+Na)^+$ Elemental Analysis Calcd. for $C_{56}H_{71}N_{10}O_{22}SNa.8H_2O$: C, 46.86; H, 6.11; N, 9.76. Found: C, 46.93; H, 5.87; N, 9.74.

EXAMPLE 56

IR (KBr): 3350, 2958, 2935, 2873, 1666, 1629, 1247, 1045 cm^{-1} NMR (DMSO-d_6, δ): 0.9–1.1 (6H, m), 1.08 (3H, d, J=6.0 Hz), 1.4–1.6 (2H, m), 1.6–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1—3.3 (1H, m), 3.6–4.5 (15H, m), 4.7–5.1 (8H, m), 5.10 (1H, d, J=5.5 Hz), 5.17 (1H, d, J=2.9 Hz), 5.25 (1H, d, J=4.5Hz), 5.55 (1H, d, J=5.7 Hz), 6.7–6.9 (3H, m), 7.0–7.5 (8H, m), 7.68 (2H, d, J=8.9 Hz), 7.73 (2H, d, J=8.3 Hz), 8.01 (2H, d, J=8.3 Hz), 8.10 (1H, d, J=8.4 Hz), 8.26 (1H, d, J=7.7 Hz), 8.8–9.0 (2H, m) FAB-MASS: m/z=1299.5 $(M+Na)^+$ Elemental Analysis Calcd. for $C_{56}H_{69}N_8O_{23}NaS.6H_2O$: C, 48.55; H, 5.89; N, 8.09. Found: C, 48.52; H, 5.94; N,8.07.

EXAMPLE 57

IR (KBr): 3355.5, 1662.3, 1629.6, 1267.0 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.8 Hz), 0.93 (3H, d, J=8.4 Hz), 0.97 (3H, d, J=6.7 Hz), 1.2–1.5 (4H, m), 1.5–1.95 (5H, m), 2.1–2.45 (4H, m), 2.5–2.7 (4H, m), 3.17 (1H, m), 3.55–4.45 (14H, m), 4.6–5.3 (13H, m), 5.56 (1H, d, J=5.6 Hz), 6.72 (1H, d, J=8.1 Hz), 6.75 (1H, s), 6.77 (1H, d, J=8.1 Hz), 7.04 (1H, s), 7.10 (1H, s), 7.2–7.45 (10H, m), 7.53 (4H, d, J=6.6 Hz), 7.85 (1H, d, J=7 Hz), 7.92 (1H, d, J=7 Hz), 8.05 (1H, d, J=7 Hz), 8.22 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1408 (M+Na)

EXAMPLE 58

IR (KBr): 3347.8, 1664.3, 1631.5, 1245.8 cm^{-1} NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.96 (3H, d, J=6.6 Hz), 1.04 (3H, d, J=5.7 Hz), 1.15–2.6 (21H, m), 3.16 (1H, m), 3.5–4.5 (16H, m), 4.6–5.4 (13H, m), 5.47 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz) 6.78–6.85 (4H, m), 7.05 (1H, s), 7.10 (1H, s), 7.18 (2H, d, J=8.6 Hz), 7.25–7.45 (6H, m), 7.72 (1H, d, J=7 Hz), 7.91 (1H, d, J=7 Hz), 8.05 (1H, d, J=9.3 Hz), 8.20 (1H, d, J=7 Hz), 8.85 (1H, s) FAB-MASS: m/z=1390 (M+Na) Elemental Analysis Calcd. for

$C_{60}H_{82}N_9O_{24}SNa.5H_2O$: C, 49.41; H, 6.36; N, 8.64. Found: C, 49.77; H, 6.71; N, 8.71.

EXAMPLE 59

IR (KBr): 3353.6, 1670.1, 1627.6, 1247.7 cm^{-1} NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.5 Hz), 0.97 (3H, d, J=6.8 Hz), 1.01 (3H, d, J=5.4 Hz), 1.1–1.55 (12H, m), 1.55–1.95 (5H, m), 2.05–4.7 (4H, m), 3.16 (1H, m), 3.5–4.5 (16H, m), 4.6–5.3 (13H, m), 5.55 (1H, d, J=5.6Hz), 6.7–6.9 (5H, m), 7.05 (1H, s), 7.1 (1H, s), 7.15 (1H, d, J=8.5 Hz), 7.25–7.5 (6H, m), 7.73 (1H, d, J=8.4 Hz), 7.92 (1H, d, J=7 Hz), 8.08 (1H, d, J=8.4 Hz), 8.18 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1390 (M+Na)

EXAMPLE 60

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.6 Hz), 0.96 (3H, d, J=6.6 Hz), 1.05 (3H, d, J=5.6 Hz), 1.1–1.5 (22H, m), 1.5–2.5 (9H, m), 2.5–3.5 (4H, m), 3.5–4.45 (14H, m), 4.45–5.45 (12H, m), 6.72 (1H, d, J=8.2 Hz), 6.79 (1H, s), 6.81 (1H, d, J=8.2 Hz), 7.04 (1H, s), 7.05–7.5 (8H, m), 7.9–8.3 (3H, m), 8.84 (1H, s) FAB-MASS: m/z=1325 (M+Na) Elemental Analysis Calcd. for $C_{58}H_{89}N_8O_{22}SNa.6H_2O$: C, 49.35; H, 7.14; N, 7.94. Found: C, 49.33; H, 7.04; N, 7.87.

EXAMPLE 61

IR (KBr): 3400, 1668.1, 1629.6, 1270.0 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.8 Hz), 1.06 (3H, d, J=5.7 Hz), 1.1–2.0 (33H, m), 2.1–2.5 (4H, m), 3.20 (3H, s), 3.28 (2H, t, J=6.5 Hz), 3.1–3.3 (1H, m), 3.6–4.45 (14H, m), 4.6–5.3 (13H, m), 5.49 (1H, d, J=6.1 Hz), 6.70 (1H, s), 6.72 (1H, d, J=8.2 Hz), 6.80 (1H, d, J=8.2 Hz), 7.03 (1H, s), 7.0–7.1 (1H, m), 7.15 (1H, s), 7.2–7.45 (6H, m), 8.0–8.3 (3H, m), 8.83 (1H, s) FAB-MASS: m/z=1426 (M+Na) Elemental Analysis Calcd. for $C_{62}H_{94}N_9O_{24}SNa.5H_2O$: C, 49.82; H, 7.01; N, 8.43. Found: C, 49.86; H, 7.31; N, 8.40.

EXAMPLE 62

IR (KBr): 3355.5, 1668.1, 1629.6, 1274.7 cm^{-1} NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.9 Hz), 1.1–2.6 (34H, m), 3.2 (1H, m), 3.6–4.55 (14H, m), 4.7–5.3 (11H, m), 5.47 (1H, d, J=5.9 Hz), 6.72 (1H, d, J=8.1 Hz), 6.79 (1H, s), 6.81 (1H, d, J=8.1 Hz), 7.05 (1H, s), 7.11 (1H, s), 7.2–7.5 (2H, m), 8.0–8.15 (2H, m), 8.20 (1H, d, J=8.0 Hz), 8.84 (1H, s) FAB-MASS: m/z=1235 (M+Na) Elemental Analysis Calcd. for $C_{51}H_{81}N_8O_{22}SNa.7H_2O$: C, 45.73; H, 7.15; N, 8.37. Found: C, 45.55; H, 7.24; N, 8.23.

EXAMPLE 63

IR (KBr): 3353.6, 1664.3, 1627.6 cm^{-1} NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.95 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.7 Hz),1.2–2.7 (30H, m), 3.16 (1H, m), 3.6–4.5 (13H, m), 4.7–5.3 (11H, m), 5.51 (1H, d, J=6.0 Hz), 5.74 (1H, s), 6.72 (1H, d, J=8.2 Hz), 6.75 (1H, s), 6.77 (1H, d, J=8.2 Hz), 7.05 (1H, s), 7.2–7.5 (3H, m), 8.0–8.3 (3H, m), 8.85 (1H, s) FAB-MASS: m/z=1204 (M+Na) Elemental Analysis Calcd. for $C_{50}H_{77}N_8O_{21}SNa.5H_2O$: C, 47.24; H, 6.90; N, 8.81. Found: C, 46.98; H, 7.12; N, 8.72.

EXAMPLE 64

Major Product

IR (KBr): 3400, 1675.8, 1631.5, 1511.9, 1234.2 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.05 (3H, d, J=5.8 Hz), 1.2–1.6 (10H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.05–3.2 (4H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.3–3.5 (5H, m), 3.6–4.5 (15H, m), 4.7–5.3 (11H, m), 5.50 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.1 (9H, m), 7.2–7.5 (3H, m), 7.81 (2H, d, J=8.6 Hz), 8.08 (1H, d, J=8.2 Hz), 8.24 (1H, d, J=7 Hz), 8.44 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1403 (M+Na) Elemental Analysis Calcd. for $C_{61}H_{85}N_{10}O_{23}SNa.9H_2O$: C, 47.47; H, 6.73; N, 9.07. Found: C, 47.43; H, 7.06; N, 9.03.

Minor Product

IR (KBr): 3350, 1668.1, 1631.5, 1511.9, 1234.2 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.07 (3H, d, J=5.8 Hz), 1.2–1.5 (6H, m), 1.55–2.1 (7H, m), 2.1–2.65 (4H, m), 3.0–3.6 (9H, m), 3.7–4.5 (15H, m), 4.7–5.6 (14H, m), 5.7–6.0 (1H, m), 6.72 (1H, d, J=8.0 Hz), 6.75–7.1 (9H, m), 7.25–7.5 (3H, m), 7.81 (2H, d, J=8.3 Hz), 8.08 (1H, d, J=8.2 Hz), 8.25 (1H, d, J=7 Hz), 8.45 (1H, d, J=7 Hz), 8.85 (1H, s) FAB-MASS: m/z=1371 (M+Na) Elemental Analysis Calcd. for $C_{60}H_{81}N_{10}O_{22}SNa.8H_2O$: C, 48.25; H, 6.55; N, 9.38. Found: C, 48.10; H, 6.81; N, 9.40.

EXAMPLE 65

IR (KBr): 3450, 1668.1, 1635.3 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=6 Hz), 1.2–1.5 (6H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.1–3.4 (9H, m), 3.6–4.5 (15H, m), 4.7–5.3 (11H, m), 5.49 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (2H, m), 6.83 (2H, d, J=9.0 Hz), 6.94 (2H, d, J=9.0 Hz), 7.04 (1H, s), 7.12 (1H, t, J=8.4 Hz), 7.2–7.5 (3H, m), 7.65–7.8 (2H, m), 8.09 (1H, d, J=8.4 Hz), 8.25 (1H, d, J=7 Hz), 8.63 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1363 (M+Na) Elemental Analysis Calcd. for $C_{58}H_{78}FN_{10}O_{22}SNa.5H_2O$: C, 48.67; N, 6.20; N, 9.79. Found: C, 48.83; H, 6.15; N, 9.74.

EXAMPLE 66

IR (KBr): 3400, 1668.1, 1635.3, 1510.0, 1240.0 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 1.2–1.5 (6H, m), 1.5–2.05 (5H, m), 2.1–2.65 (4H, m), 3.1–3.3 (9H, m), 3.6–4.5 (15H, m), 4.7–5.3 (11H, m), 5.51 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (4H, m), 6.94 (2H, d, J=9.2 Hz), 7.04 (1H, s), 7.24 (1H, d, J=8.5 Hz), 7.15–7.5 (3H, m), 7.86 (1H, dd, J=8.6 and 2.1 Hz), 8.02 (1H, d, J=2.1 Hz), 8.04 (1H, d, J=8.4 Hz), 8.23 (1H, d, J=7 Hz), 8.70 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1379 (M+Na) Elemental Analysis Calcd. for $C_{58}H_{78}ClN_{10}O_{22}SNa.6H_2O$: C, 47.52; H, 6.19; N, 9.55. Found: C, 47.78; H, 6.23; N, 9.55.

EXAMPLE 67

IR (KBr): 3400, 1670 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.05 (3H, d, J=5.7 Hz), 1.4–2.65 (17H, m), 2.65–3.6 (8H, m), 3.6–4.5 (15H, m), 4.6–5.3 (11H, m), 5.44 (1H, d, J=6.0 Hz), 6.73 (1H, d, J=8.2 Hz), 6.81 (1H, s), 6.83 (1H, d, J=8.2 Hz), 6.98 (2H, d, J=8.9 Hz), 7.05 (1H, s), 7.2–7.5 (3H, m), 7.80 (2H, d, J=8.9 Hz), 8.05 (1H, d, J=8.4 Hz), 8.26 (1H, d, J=7 Hz), 8.39 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1229 (M+Na) Elemental Analysis Calcd. for $C_{52}H_{74}N_{10}O_{21}S.5H_2O$: C, 48.14; H, 6.53; N, 10.80. Found: C, 48.29; H, 6.33; N, 10.95.

EXAMPLE 68

IR (KBr): 3400, 1652.7, 1635.3, 1511.9, 1241.9 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.7 Hz), 1.2–1.5 (6H, m), 1.6–2.0 (5H, m), 2.1–2.6 (4H, m), 3.0–3.3 (5H, m), 3.6–4.6 (19H, m), 4.7–5.3 (11H, m), 5.53 (1H, d, J=5.6 Hz), 6.73 (1H, d, J=8.2 Hz), 6.75–7.0 (2H, m), 6.83 (2H, d, J=9.2 Hz), 6.95

(2H, d, J=9.2 Hz), 7.05 (1H, s), 7.12 (1H, s), 7.25–7.5 (2H, m), 7.42 (1H, d, J=9.5 Hz), 7.84 (1H, d, J=9.5 Hz), 7.9–8.1 (2H, m), 8.71 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1347 (M+Na) Elemental Analysis Calcd. for $C_{56}H_{77}N_{12}O_{22}SNa.7H_2O$: C, 46.34; H, 6.32; N, 11.58. Found: C, 46,38, H, 6.18; N, 11.36.

EXAMPLE 69

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.8 Hz), 1.2–1.5 (6H, m), 1.6–2.05 (5H, m), 2.1–2.6 (4H, m), 3.0–3.3 (5H, m), 3.4–3.55 (4H, m), 3.7–4.6 (15H, m), 4.7–5.3 (11H, m), 5.52 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.1 Hz), 6.8–6.95 (2H, m), 6.83 (2H, d, J=9.3 Hz), 6.95 (2H, d, J=9.3 Hz), 7.05 (1H, s), 7.14 (1H, s), 7.3–7.6 (3H, m), 7.84 (1H, d, J=8.6 Hz), 7.95–8.1 (2H, m), 8.40 (1H, s), 8.42 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1346 (M+Na) Elemental Analysis Calcd. for $C_{57}H_{78}N_{11}O_{22}SNa.5H_2O$: C, 48.40; H, 6.27; N, 10.89. Found: C, 48.32, H, 6.44; N, 10.86.

EXAMPLE 70

IR (KBr): 3400, 1668.1, 1629.6, 1511.9 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.7 Hz), 1.15–1.5 (6H, m), 1.6–2.0 (7H, m), 2.1–2.65 (5H, m), 3.1–3.5 (9H, m), 3.6–4.5(13H, m), 4.7–5.3 (11H, m), 5.46 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.81 (1H, s), 6.84 (1H, d, J=8.2 Hz), 6.91 (2H, d, J=8.7 Hz), 6.95–7.05 (3H, m), 7.09 (2H, d, J=8.7 Hz), 7.25–7.5 (3H, m), 7.81 (2 H, d, J=8.8 Hz), 8.09 (1H, d, J=7 Hz), 8.25 (1H, d, J=7 Hz), 8.04 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1327 (M+Na) Elemental Analysis Calcd. for $C_{58}H_{77}N_{10}O_{21}SNa.5H_2O$: C, 49.92; H, 6.28; N, 10.03. Found: C, 49.75; H, 6.41; N, 10.25.

EXAMPLE 71

IR (KBr): 3350, 1668.1, 1629.6, 1511.9, 1232.3 cm^{-1} NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=6.0 Hz), 1.2–1.4 (6H, m), 1.4–1.6 (2H, m), 1.7–2.1 (3H, m), 2.1–2.7 (6H, m), 3.1–3.5 (9H, m), 3.72 (2H, m), 3.8–4.5 (11H, m), 4.7–5.3 (11H, m), 5.47 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (2H, m), 6.91 (2H, d, J=8.6 Hz), 6.95–7.15 (5H, m), 7.25–7.5 (3H, m), 7.81 (2H, d, J=8.8 Hz), 8.09 (1H, d, J=8.4 Hz), 8.26 (1H, d, J=7 Hz), 8.40 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1329 (M+Na) Elemental Analysis Calcd. for $C_{58}H_{79}N_{10}NaO_{21}S.6H_2O$: C, 49.22; H, 6.48; N, 9.90. Found: C, 49.33; H, 6.67; N, 9.89.

EXAMPLE 72

IR (KBr): 3450, 1668.1, 1631.5, 1240.0 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.05 (3H, d, J=5.6 Hz), 1.3–1.7 (4H, m), 1.7–2.1 (7H, m), 2.1–2.73 (6H, m), 2.75–3.05 (4H, m), 3.05–4.5 (18H, m), 4.7–5.5 (12H, m), 6.72 (1H, d, J=8.3 Hz), 6.77–6.9 (2H, m), 6.96 (2H, d, J=8.6 Hz), 7.05 (1H, s), 7.1–7.5 (8H, m), 7.80 (2H, d, J=8.6 Hz), 8.06 (1H, d, J=8.4 Hz), 8.28 (1H, d, J=7 Hz), 8.41 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1305 (M+Na) Elemental Analysis Calcd. for $C_{58}H_{78}N_{10}O_{21}S.8H_2O$: C, 48.80; H, 6.64; N, 9.81. Found: C, 48.88; H, 6.50; N, 9.81.

EXAMPLE 73

IR (KBr): 1673.9, 1646.9, 1510.0, 1238.1 cm^{-1} NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.4 Hz), 0.96 (3H, d, J=6.6 Hz), 1.05 (3H, d, J=5.6 Hz), 1.2–1.5 (6H, m), 1.5–2.0 (9H, m), 2.1–2.8 (11H, m), 3.1–3.4 (5H, m), 3.4–4.5 (17H, m), 4.6–5.5 (12H, m), 6.6–7.0 (9H, m), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.78 (2H, d, J=8.7 Hz), 8.05 (1H, d, J=8.4 Hz), 8.24 (1H, d, J=7 Hz), 8.39 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-MASS: m/z=1326 (M^+—SO_3Na) Elemental Analysis Calcd. for $C_{63}H_{89}N_{11}O_{22}S.9H_2O$ C, 48.92; H, 6.97; N, 9.96. Found: C, 48.77; H, 6.73; N, 9.94.

EXAMPLE 74

IR (KBr): 3450, 1670.1, 1631.5, 1280.5 cm^{-1} NMR (DMSO-d_6, δ): 0.87 (3H, t, J=7.0 Hz), 0.96 (3H, t, J=6.8 Hz), 1.05 (3H, d, J=5.6 Hz), 1.1–1.65 (13H, m), 1.65–2.1 (7H, m), 2.1–2.65 (5H, m), 3.17 (1H, m), 3.6–4.5 (13H, m), 4.7–5.3 (11H, m), 5.49 (1H, d, J=5.9 Hz), 6.72 (1H, d, J=8.2), 6.82 (1H, d, J=8.2 Hz), 6.84 (1H, s), 7.04 (1H, s), 7.29 (2H, d, J=8.3 Hz), 7.2–7.5 (3H, m), 7.80 (2H, d, J=8.3 Hz), 8.10 (1H, d, J=8.4 Hz), 8.26 (1H, d, J=7 Hz), 8.65 (1H, d, J=7 Hz), 8.84 (1H, s) FAB-Mass: m/z=1237 (M+Na) Elemental Analysis Calcd. for $C_{53}H_{75}N_8O_{21}SNa.6H_2O$: C, 48.10; H, 6.63; N, 8.47. Found: C, 48.26; H, 6.62; N, 8.46.

EXAMPLE 75

IR (KBr): 3400, 1670.1, 1627.6, 1272.8 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=3.3 Hz), 1.08 (3H, d, J=7.5 Hz), 1.2–1.6 (10H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.0–3.3 (1H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.73 (2H, m), 3.9–4.6 (13H, m), 4.7–5.3 (11H, m), 5.53 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.3 Hz), 6.83 (1H, d, J=8.3 Hz), 6.91 (1H, s), 7.05 (1H, s), 7.23 (1H, dd, J=9.0 and 2.3 Hz), 7.3–7.5 (4H, m), 7.8–8.0 (3H, m), 8.09 (1H, d, J=8.4 Hz), 8.33 (1H, d, J=7 Hz), 8.44 (1H, s), 8.80 (1H, d, J=7 Hz), 8.85 (1H, s) FAB-MASS: m/z=1293 (M+Na) Elemental Analysis Calcd. for $C_{55}H_{75}N_8O_{23}SNa.6H_2O$: C, 47.89; H, 6.36; N, 8.12. Found: C, 47.81; H, 6.26; N, 8.05.

EXAMPLE 76

IR (KBr): 3361.3, 1668.1, 1635.3, 1627.6 cm^{-1} NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.8 Hz), 1.19–1.25 (8H, m), 1.25–2.00 (5H, m), 2.02–2.53 (4H, m), 2.44 (3H, s), 2.61 (2H, t, J=7.6 Hz), 3.05–3.27 (1H, m), 3.55–4.50 (13H, m), 4.65–5.65 (12H, m), 6.42 (1H, s), 6.65–6.95 (3H, m), 7.05 (1H, d, J=0.4 Hz), 7.13–7.50 (5H, m), 7.50–7.88 (6H, m), 8.10 (1H, d, J=9.0 Hz), 8.25 (1H, d, J=8.4 Hz), 8.40 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1299.3 (M+Na−1) Elemental Analysis Calcd. for $C_{58}H_{77}N_8NaO_{21}S.5H_2O$: C, 50.94; H, 6.41; N, 8.19. Found: C, 50.99; H, 6.40; N, 8.15.

EXAMPLE 77

IR (Nujol): 3351.7, 1670.1, 1652.7, 1623.8 cm^{-1} NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.8 Hz), 1.13–1.45 (8H, m), 1.47–1.96 (5H, m), 2.06–2.66 (8H, m), 2.81 (2H, t, J=7.6 Hz), 3.04–3.30 (1H, m), 3.53–4.50 (13H, m), 4.53–5.70 (12H, m), 6.64–6.88 (3H, m), 7.04 (1H, d, J=0.4 Hz), 7.13–7.60 (11H, m), 8.10 (1H, d, J=9.0 Hz), 8.18 (1H, d, J=8.4 Hz), 8.30 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1287.4 (M+Na−1) Elemental Analysis Calcd. for $C_{57}H_{77}N_8NaO_{21}S.5H_2O$: C, 50.51; H, 6.46; N, 8.27. Found: C, 50.84; H, 6.60; N, 8.33.

EXAMPLE 78

IR (KBr): 3361.3, 1683.6, 1670.1, 1662.3, 1652.7, 1646.9, 1635.3, 1627.6, 1623.8 cm^{-1} NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.6 Hz), 1.28–2.00 (13H, m), 2.08–2.60 (4H, m), 3.07–3.30 (1H, m), 3.60–4.66

(17H, m), 4.66–5.12 (9H, m), 5.11 (1H, d, J=3.1 Hz), 5.25 (1H, d, J=4.6 Hz), 5.52 (1H, d, J=6.0 Hz), 6.62–6.95 (4H, m), 6.95–7.15 (3H, m), 7.20–7.50 (3H, m), 7.50–7.85 (7H, m), 8.12 (1H, d, J=8.4 Hz), 8.35 (1H, d, J=7.7 Hz), 8.53 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1319.7 (M+Na-1) Elemental Analysis Calcd. for $C_{57}H_{74}N_8NaO_{22}SF.8H_2O$: C, 47.49; H, 6.29; N, 7.77. Found: C, 47.79; H, 6.16; N, 7.93.

EXAMPLE 79

IR (KBr): 3354.9, 1668.1, 1662.3, 1654.6, 1646.9, 1627.6 cm^{-1} NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 0.90–1.10 (6H, m), 1.10–1.40 (8H, m), 1.48–1.95 (5H, m), 2.05–2.46 (4H, m), 2.60 (2H, t, J=7.6 Hz), 3.07–3.23 (1H, m), 3.55–4.45 (14H, m), 4.67–5.32 (11H, m), 5.48–5.63 (1H, m), 6.22 (1H, , J=5.3 Hz), 6.65–6.89 (3H, m), 6.97–7.15 (2H, m), 7.20–7.68 (10H, m), 7.85–8.20 (3H, m), 8.84 (1H, s) FAB-MASS: m/z=1289.4 (M+Na-1) Elemental Analysis Calcd. for $C_{56}H_{75}N_8NaO_{22}S.3H_2O$: C, 50.90; H, 6.18; N, 8.48. Found: C, 50.80; H, 6.44; N, 8.29.

EXAMPLE 80

IR (KBr): 3361.3, 1664.3, 1631.5, 1600.6 cm^{-1} NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.98 (3H, d, J=6.7 Hz), 1.16 (3H, t, J=5.9 Hz), 1.20–1.45 (8H, m), 1.50–1.70 (2H, m), 1.70–2.05 (3H, m), 2.10–2.57 (4H, m), 2.63 (2H, t, J=7.6 Hz), 3.10–3.30 (1H, m), 3.68–4.50 (13H, m), 4.78–5.32 (11H, m), 5.66 (1H, d, J=5.7 Hz), 6.68–7.02 (3H, m), 7.04 (1H, d, J=0.4 Hz), 7.25–7.48 (4H, m), 7.60–8.08 (7H, m), 8.10 (1H, d, J=8.4 Hz), 8.28 (1H, d, J=7.7 Hz), 8.85 (1H, s), 9.30 (1H, d, J=7.1 Hz) FAB-MASS: m/z=1287.5 (M+Na-1) Elemental Analysis Calcd. for $C_{55}H_{73}N_8NaO_{22}S.3H_2O$: C, 50.53; H, 6.09; N, 8.57. Found: C, 50.66; H, 6.01; N, 8.22.

EXAMPLE 81

IR (KBr): 3349.7, 1668.1, 1627.6 cm^{-1} NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.8 Hz), 1.18–1.48(8H, m), 1.50–2.10 (5H, m), 2.10–2.45 (3H, m), 2.50–2.65 (1H, m), 2.77 (2H, t, J=7.6 Hz), 3.05–3.25 (1H, m), 3.60–4.65 (13H, m), 4.67–5.60 (12H, m), 6.65–6.97 (3H, m), 7.05 (1H, d, J=0.4 Hz), 7.21–7.43 (4H, m), 7.76 (1H, s), 7.83–8.05 (3H, m), 8.10 (1H, d, J=9.0 Hz), 8.29 (1H, d, J=8.4 Hz), 8.48 (1H, s), 8.64–9.03 (2H, m) FAB-MASS: m/z=1233.0 (M+Na-1) Elemental Analysis Calcd. for $C_{53}H_{71}N_8NaO_{20}S.3H_2O$: C, 50.96; H, 6.22; N, 8.96. Found: C, 50.62; H, 6.40; N, 8.92.

EXAMPLE 82

IR (KBr): 3361.3, 1670.1, 1627.6 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.9 Hz), 1.18–1.43 (6H, m), 1.50–2.10 (5H, m), 2.10–2.69 (4H, m), 2.77 (2H, t, J=7.6 Hz), 3.07–3.29 (1H, m), 3.60–4.62 (13H, m), 4.69–5.23 (10H, m), 5.27 (1H, d, J=4.5 Hz), 5.55 (1H, d, J=5.9 Hz), 6.68–7.00 (3H, m), 7.05 (1H, d, J=0.4 Hz), 7.25–7.53 (4H, m), 7.76 (1H, s), 7.84–8.05 (3H, m), 8.13 (1H, d, J=8.4 Hz), 8.33 (1H, d, J=7.7 Hz), 8.48 (1H, s), 8.73–9.00 (2H, m) FAB-MASS: m/z=1219.4 (M+Na-1) Elemental Analysis Calcd. for $C_{52}H_{69}N_8NaO_{21}S.5H_2O$: C, 48.51; H, 6.19; N, 8.71. Found: C, 48.67; H, 6.34; N, 8.74.

EXAMPLE 83

IR (KBr): 3357.5, 1668.1, 1627.6 cm^{-1} NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=6.0 Hz), 1.20–1.62 (10H, m), 1.62–2.00 (5H, m), 2.10–2.65 (4H, m), 3.20 (3H, s), 3.08–3.45 (1H, m), 3.28 (2H, t, J=6.5 Hz), 3.53–4.50 (15H, m), 4.68–5.13 (9H, m), 5.17 (1H, d, J=3.1 Hz), 5.25 (1H, d, J=4.4 Hz), 5.53 (1H, d, J=6.0 Hz), 6.68–6.95 (4H, m), 6.95–7.11 (3H, m), 7.20–7.52 (3H, m), 7.55–7.95 (7H, m), 8.13 (1H, d, J=8.4 Hz), 8.30 (1H, d, J=7.7 Hz), 8.52 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1345.2 (M+Na-1) Elemental Analysis Calcd. for $C_{59}H_{79}N_8NaO_{23}S.8H_2O$: C, 48.29; H, 6.53; N, 7.64. Found: C, 48.44; H, 6.58; N, 7.75.

EXAMPLE 84

IR (KBr): 3353.6, 1662.3, 1627.6 cm^{-1} NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.5 Hz), 1.40–1.65 (2H, m), 1.65–2.00 (5H, m), 2.00–2.67 (6H, m), 3.08–3.30 (1H, m), 3.50–4.50 (15H, m), 4.68–5.13 (11H, m), 5.18 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.5 Hz), 5.53 (1H, d, J=6.0 Hz), 5.70–6.00 (1H, m), 6.63–6.95 (4H, m), 6.95–7.13 (3H, m), 7.20–7.52 (3H, m), 7.52–7.95 (7H, m), 8.12 (1H, d, J=8.4 Hz), 8.31 (1H, d, J=7.7 Hz), 8.53 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1285.4 (M+Na-1) Elemental Analysis Calcd. for $C_{56}H_{71}N_8O_{22}SNa.8H_2O$: C, 47.79; H, 6.23; N, 7.96. Found: C, 47.59; H, 6.32; N, 8.06.

EXAMPLE 85

IR (KBr): 3363.2, 1670.1, 1627.6 cm^{-1} NMR (DMSO-d_6, δ): 0.89 (6H, d, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.7 Hz), 1.22–1.41 (2H, m), 1.50–1.97 (6H, m), 2.11–2.65 (4H, m), 3.10–3.30 (1H, m), 3.60–4.50 (15H, m), 4.70–5.08 (8H, m), 5.10 (1H, d, J=5.6 Hz), 5.16 (1H, d, J=3.1 Hz), 5.25 (1H, d, J=4.5 Hz), 5.50 (1H, d, J=5.9 Hz), 6.65–6.92 (4H, m), 6.92–7.12 (3H, m), 7.21–7.50 (3H, m), 7.52–7.90 (7H, m), 8.12 (1H, d, J=8.4 Hz), 8.30 (1H, d, J=7.7 Hz), 8.56 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1287.6 (M+Na-1) Elemental Analysis Calcd. for $C_{56}H_{73}N_8NaO_{22}S.6.5H_2O$: C, 48.66; H, 6.27; N, 8.11. Found: C, 48.67; H, 6.32; N, 8.20.

EXAMPLE 86

IR (KBr): 3361.3, 1683.6, 1670.1, 1654.6, 1635.3, 1623.8 cm^{-1} NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.6 Hz), 1.30–2.00 (11H, m), 2.10–2.70 (4H, m), 3.05–3.15 (1H, m), 3.55–4.70 (17H, m), 4.70–5.11 (9H, m), 5.16 (1H, d, J=3.1 Hz), 5.25 (1H, d, J=4.5 Hz), 5.52 (1H, d, J=6.0 Hz), 6.65–6.95 (4H, m), 6.95–7.10 (3H, m), 7.10–7.50 (3H, m), 7.50–7.85 (7H, m), 8.12 (1H, d, J=8.4 Hz), 8.30 (1H, d, J=8.3 Hz), 8.52 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1305.2 (M+Na-1) Elemental Analysis Calcd. for $C_{56}N_{72}N_8NaO_{22}SF.6H_2O$: C, 48.34; H, 6.09; N, 8.05. Found: C, 48.47; H, 6.29; N, 7.95.

EXAMPLE 87

IR (KBr): 3359.4, 1668.1, 1654.6, 1625.7 cm^{-1} NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=6.0 Hz), 1.22–1.62 (6H, m), 1.62–2.00 (5H, m), 2.10–2.65 (4H, m), 3.20 (3H, s), 3.05–3.40 (1H, m), 3.31 (2H, t, J=6.5 Hz), 3.60–4.55 (15H, m), 4.65–5.13 (9H, m), 5.16 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.4 Hz), 5.53 (1H, d, J=6.0 Hz), 6.68–6.95 (4H, m), 6.95–7.20 (3H, m), 7.20–7.58 (3H, m), 7.58–7.90 (7H, m), 8.13 (1H, d, J=8.4 Hz), 8.32 (1H, d, J=7.7 Hz), 8.53 (1H, d, J=7.0 Hz), 8.85 (1H, s) FAB-MASS: m/z=1317.6 (M+Na-1) Elemental Analysis Calcd. for $C_{57}H_{75}N_8NaO_{23}S.7H_2O$: C, 48.16; H, 6.31; N, 7.88. Found: C, 48.21; H, 6.60; N, 7.78.

EXAMPLE 88

IR (KBr): 3350, 2954, 1668, 1629, 1538, 1511, 1454, 1249 cm^{-1} NMR (DMSO-d_6, δ): 0.88 (3H, t, J=7.1 Hz), 0.96

(3H, d, J=7.5 Hz), 1.08 (2H, d, J=5.7 Hz), 1.2–1.5 (6H, m), 1.6–2.4 (8H, m), 2.6–2.7 (1H, m), 3.1–3.3 (1H, m), 3.6–4.5 (19H, m), 4.7–5.3 (8H, m), 6.73 (1H, d, J=8.2 Hz), 6.8–7.1 (5H, m), 7.19 (1H, s), 7.3–7.5 (3H, m), 7.75 (2H, d, J=8.7 Hz), 7.8–8.0 (4H, m), 8.08 (1H, d, J=8.9 Hz), 8.30 (1H, d, J=7.7 Hz), 8.7–9.0 (3H, m) FAB-MASS: m/z=1327 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{57}H_{73}N_{10}O_{22}NaS.9H_2O$: C 46.65, H 6.25, N 9.54 Found: C 46.95, H 6.22, N 9.55

EXAMPLE 89

IR (KBr): 3376, 2931, 2858, 1662, 1631, 1521, 1444, 1245, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.9Hz), 1.3–1.6 (6H, m), 1.7–2.1 (5H, m), 2.2–2.4 (3H, m), 2.5–2.6 (1H, m), 3.21 (3H, s), 3.2–3.4 (3H, m), 3.6–4.5 (16H, m), 4.79 (2H, d, J=6.0Hz), 4.9–5.2 (5H, m), 5.10 (1H, d, J=3.6Hz), 5.18 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.5Hz), 5.53 (1H, d, J=6.0Hz), 6.73 (1H, d, J=8.2Hz), 6.8–7.0 (2H, m), 7.0–7.2 (3H, m), 7.3–7.5 (3H, m), 7.6–7.9 (8H, m), 8.01 (2H, d, J=8.4Hz), 8.12 (1H, d, J=8.4Hz), 8.31 (1H, d, J=7.7Hz), 8.79 (1H, d, J=7.0Hz), 8.85 (1H, s)

FAB-MASS: m/z=1367 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{61}H_{77}N_8O_{23}NaS.6.5H_2O$: C 50.10, H 6.20, N 7.66 Found: C 50.09, H 6.17, N 7.62

EXAMPLE 90

IR (KBr): 3363, 2937, 2869, 1646, 1444, 1255 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.7Hz), 1.2–1.6 (10H, m), 1.7–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.7 (1H, m), 3.20 (3H, s), 3.2–3.4 (1H, m), 3.6–4.6 (16H, m), 4.7–5.2 (8H, m), 5.16 (1H, d, J=3.1Hz), 5.24 (1H, d, J=4.5Hz), 5.54 (1H, d, J=5.8Hz), 6.73 (1H, d, J=8.2Hz), 6.8–7.0 (2H, m), 7.1–7.4 (6H, m), 7.97 (2H, d, J=8.8Hz), 8.0–8.4 (6H, m), 8.84 (1H, s), 8.92 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1403.6 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{59}H_{77}N_{10}O_{23}NaS_2.6H_2O$: C 47.58, H 6.02, N 9.40 Found: C 47.72, H 6.12, N 9.42

EXAMPLE 91

IR (KBr): 3350, 1668, 1654, 1625, 1537, 1521, 1245, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.1 (6H, m), 1.07 (3H, d, J=5.7Hz), 1.4–2.0 (7H, m), 2.2–2.5 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.6–4.5 (16H, m), 4.7–5.1 (7H, m), 5.09 (1H, d, J=5.6Hz), 5.16 (1H, d, J=3.1Hz), 5.25 (1H, d, J=4.4Hz), 5.53 (1H, d, J=6.0Hz), 6.73 (1H, d, J=8.4Hz), 6.8–7.2 (6H, m) 7.2–7.5 (4H, m), 7.5–7.8 (6H, m), 8.11 (1H, d, J=8.4Hz), 8.32 (1H, d, J=7.7Hz), 8.54 (1H, d, J=7.0Hz), 8.84 (1H, s)

FAB-MASS: m/z=1259 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{54}H_{69}N_8O_{22}NaS.8H_2O$: C 46.95, H 6.20, N 8.11 Found: C 47.20, H 6.23, N 8.28

EXAMPLE 92

IR (KBr): 3359, 2929, 2852, 1668, 1650, 1631, 1538, 1515 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, J=6.7Hz), 1.09 (3H, d, J=6.1Hz), 1.2–1.6 (5H, m), 1.6–2.5 (10H, m), 2.5–2.6 (1H, m), 3.18 (1H, m), 3.7–4.5 (15H, m), 4.8–5.2 (8H, m), 5.17 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.5Hz), 5.55 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.1Hz), 6.81 (1H, s), 6.85 (1H, s), 7.05 (1H, s), 7.2–7.4 (3H, m), 7.45 (2H, d, J=8.2Hz), 7.96 (2H, d, J=8.2Hz), 8.0–8.2 (4H, s), 8.2–8.3 (1H, m), 8.85 (1H, s), 8.9–9.0 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1327.5 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{56}H_{69}N_{10}O_{21}S_2Na.6H_2O$: C 47.59, H 5.78, N 9.91

EXAMPLE 93

IR (KBr): 3350, 1654, 1629, 1517, 1249, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.1 (6H, m), 1.11 (3H, d, J=5.9Hz), 1.6–2.0 (5H, s), 2.1–2.4 (3H, s), 2.6–2.7 (1H, m), 3.1–3.3 (1H, m), 3.6–4.5 (16H, m), 4.7–5.2 (7H, m), 5.10 (1H, d, J=5.6Hz), 5.17 (1H, d, J=3.1Hz), 5.25 (1H, d, J=4.5Hz), 5.55 (1H, d, J=5.7Hz), 6.7–6.9 (3H, m), 7.0–7.5 (6H, m), 7.74 (2H, d, J=8.8Hz), 7.91 (2H, d, J=8.5Hz), 8.1–8.4 (8H, m), 8.84 (1H, s), 8.97 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1363.5 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{59}H_{69}N_{10}O_{23}SNa.5H_2O$: C 49.51, H 5.56, N 9.79 Found: C 49.39, H 5.63, N 9.77

EXAMPLE 94

IR (KBr): 3355, 2929, 2856, 1664, 1631, 1519, 1440, 1282 cm^{-1}

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.7Hz), 1.07 (3H, t, J=5.8Hz), 1.2–1.5 (12H, m), 1.7–2.0 (5H, m), 2.2–2.4 (3H, m), 2.5–2.7 (1H, m), 2.94 (2H, t, J=7.4Hz), 3.1–3.3 (1H, m), 3.6–4.6 (14H, m), 4.8–5.2 (7H, m), 5.10 (1H, d, J=3.6Hz), 5.17 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.5Hz), 5.55 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.2Hz), 6.8–7.0 (2H, m), 7.0–7.5 (4H, m), 8.0–8.2 (5H, m), 8.27 (1H, d, J=7.7Hz), 8.85 (1H, s), 8.93 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1279 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{53}H_{73}N_{10}O_{22}SNa.5.5H_2O$: C 46.93, H 6.24, N 10.33 Found: C 46.93, H 6.46, N 10.31

EXAMPLE 95

IR (KBr): 3363, 1673, 1648, 1538, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 0.92 (3H, t, J=6.8Hz), 0.97 (3H, d, J=6.8Hz), 1.10 (3H, d, J=5.8Hz), 1.2–1.5 (6H, m), 1.7–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.6–4.5 (16H, m), 4.7–5.1 (9H, m), 5.16 (1H, d, J=3.1Hz), 5.24 (1H, d, J=4.5Hz), 5.54 (1H, d, J=5.8Hz), 6.73 (1H, d, J=8.2Hz), 6.8–7.4 (8H, m), 8.04 (2H, d, J=8.8Hz), 8.13 (2H, d, J=8.6Hz), 8.2–8.4 (4H, m), 8.84 (1H, s), 8.98 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1329.6 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{56}H_{71}N_{10}O_{23}SNa.7H_2O$: C 46.92, H 5.97, N 9.77 Found: C 46.86, H 5.99, N 9.77

EXAMPLE 96

IR (KBr): 3355, 2929, 1666, 1648, 1631, 1515, 1442, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7Hz), 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d, J=5.8Hz), 1.2–1.5 (10H, m), 1.7–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.6–4.6 (16H, m), 4.79 (2H, d, J=5.9Hz), 4.8–5.2 (5H, m), 5.09 (1H, d, J=5.5Hz), 5.16 (1H, d, J=3.1Hz), 5.23 (1H, d, J=4.5Hz), 5.53 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.0Hz), 6.8–6.9 (2H, m), 7.0–7.5 (6H, m), 7.97 (2H, d, J=8.8Hz), 8.0–8.3 (6H, m), 8.83 (1H, s), 8.88 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1373.5 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{58}H_{75}N_{10}O_{22}S_2Na.6H_2O$: C 47.73, H 6.01, N 9.60 Found: C 47.57, H 5.92, N 9.53

EXAMPLE 97

IR (KBr): 3361, 2925, 2852, 1668, 1650, 1631, 1538, 1452, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.9Hz), 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.7Hz), 1.2–1.4 (11H, m), 1.4–1.6 (2H, m), 1.7–2.1 (5H, m), 2.1–2.5 (5H, m), 2.5–2.6 (1H, m), 3.1–3.3 (2H, m), 3.7–4.5 (14H, m), 4.7–5.0 (7H, m), 5.09 (1H, d, J=5.6Hz), 5.16 (1H, d, J=3.1Hz), 5.25 (1H, d, J=4.5Hz), 5.54 (1H, d, J=5.8Hz), 6.73 (1H, d, J=8.2Hz), 6.8–7.0 (2H, d), 7.04 (1H, s), 7.2–7.5 (3H, m), 8.03 (4H, s), 8.0–8.3 (2H, m), 8.84 (1H, s), 8.95 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1321.9 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{55}H_{75}N_{10}O_{21}S_2Na.5H_2O$: C 47.54, H 6.17, N 10.08 Found: C 47.38, H 6.12, N 9.98

EXAMPLE 98

IR (KBr): 3374, 2937, 2875, 1658, 1629, 1531, 1436, 1255, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.11 (6H, m), 1.09 (3H, d, J=5.7Hz), 1.2–1.5 (4H, m), 1.7–2.1 (5H, m), 2.2–2.5 (3H, m), 2.6–2.7 (1H, m), 3.2–3.3 (1H, m), 3.6–4.5 (16H, m), 4.80 (2H, d, J=5.8Hz), 4.8–5.2 (5H, m), 5.10 (1H, d, J=5.5Hz), 5.17 (1H, d, J=3.0Hz), 5.24 (1H, d, J=4.5Hz), 5.53 (1H, d, J=5.8Hz), 6.73 (1H, d, J=8.2Hz), 6.8–7.0 (2H, m), 7.06 (1H, s), 7.10 (2H, d, J=8.9Hz), 7.2–7.5 (3H, m), 7.68 (1H, s), 7.86 (2H, d, J=8.8Hz), 8.0–8.4 (6H, m), 8.84 (1H, s), 8.90 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1314 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{56}H_{70}N_9O_{23}NaS.6H_2O$: C 48.03, H 5.90, N 9.00 Found: C 47.92, H 5.83, N 8.88

EXAMPLE 99

IR (KBr): 3345, 1646, 1633, 1531, 1257 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.11 (3H, d, J=5.7Hz), 1.2–1.6 (10H, m), 1.7–2.5 (8H, m), 2.6–2.7 (1H, m), 3.21 (3H, s), 3.3–3.4 (1H, m), 3.7–4.6 (16H, m), 4.8–5.2 (8H, m), 5.16 (1H, d, J=3.1Hz), 5.24 (1H, d, J=4.5Hz), 5.55 (1H, d, J=5.7Hz), 6.7–6.9 (3H, m), 7.0–7.5 (6H, m), 8.0–8.3 (8H, m), 8.84 (1H, s), 8.96 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1387.7 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{59}H_{77}N_{10}O_{24}NaS.6H_2O$: C 48.09, H 6.09, N 9.51 Found: C 47.81, H 5.83, N 9.38

EXAMPLE 100

IR (KBr): 3357, 1668, 1631, 1429, 1284, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.8Hz), 1.8–2.4 (6H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.7–4.6 (14H, m), 4.7–5.2 (7H, m), 5.10 (1H, d, J=5.5Hz), 5.17 (1H, d, J=3.1Hz), 5.24 (1H, d, J=5.5Hz), 5.53 (1H, d, J=5.8Hz), 6.75 (1H, d, J=8.2Hz), 6.8–6.9 (2H, m), 7.05 (1H, s), 7.3–7.6 (9H, m), 7.8–7.9 (4H, m), 8.0–8.2 (5H, m), 8.2–8.3 (1H, m), 8.34 (1H, d, J=9.3Hz), 8.7–8.8 (1H, m), 8.85 (1H, s)

FAB-MASS: m/z=1332.7 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{58}H_{65}N_{10}O_{22}SNa.8H_2O$: C 47.93, H 5.62, N 9.64 Found: C 47.83, H 5.53, N 9.56

EXAMPLE 101

IR (KBr): 3353, 2929, 2856, 1666, 1631, 1612, 1496, 1440, 1259 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.6Hz), 0.97 (3H, d, J=6.5Hz), 1.09 (3H, d, J=5.9Hz), 1.2–1.5 (10H, m), 1.7–2.1 (5H, m), 2.2–2.5 (3H, m), 2.6–2.7 (1H, m), 3.1–3.2 (1H, m), 3.6–4.5 (16H, m), 4.7–5.0 (3H, m), 5.0–5.2 (5H, m), 5.10 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.2Hz), 5.56 (1H, d, J=5.5Hz), 6.73 (1H, d, J=8.1Hz), 6.8–7.0 (2H, m), 7.05 (1H, s), 7.1–7.5 (5H, m), 8.0–84 (8H, m), 8.85 (1H, s), 8.95 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1357.3 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{58}H_{75}N_{10}O_{23}NaS.7H_2O$: C 47.67, H 6.14, N 9.58 Found: C 47.63, H 6.42, N 9.52

EXAMPLE 102

IR (KBr): 3361, 1670, 1648, 1633, 1540, 1519, 1249 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=7.0Hz), 0.97 (3H, d, J=6.8Hz), 1.10 (3H, d, J=5.7Hz), 1.2–1.5 (6H, m), 1.6–2.4 (8H, m), 2.5–2.7 (1H, m), 3.1–3.3 (1H, m), 3.6–4.5 (16H, m), 4.80 (2H, d, J=5.8Hz), 4.8–5.2 (5H, m), 5.10 (1H, d, J=5.4Hz), 5.18 (1H, d, J=3.1Hz), 5.25 (1H, d, J=4.3Hz), 5.55 (1H, d, J=5.7Hz), 6.73 (1H, d, J=8.2Hz), 6.8–7.0 (2H, m), 7.0–7.5 (6H, m), 8.02 (1H, d, J=5.3Hz), 8.0–8.4 (4H, m), 8.42 (2H, d, J=8.4Hz), 8.48 (2H, d, J=8.9Hz), 8.8–9.0 (3H, m)

FAB-MASS: m/z=1339.3 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{58}H_{73}N_{10}O_{22}SNa.6H_2O$: C 48.87, H 6.01, N 9.83 Found: C 49.16, H 5.92, N 9.86

EXAMPLE 103

IR (KBr): 3350, 2971, 2859, 1672, 1629, 1537, 1442, 1247, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J≦6.8Hz), 1.0–1.2 (6H, m), 1.2–1.6 (12H, m), 1.7–2.5 (8H, m), 2.5–2.6 (1H, m), 3.2–3.6 (7H, m), 3.7–4.5 (16H, m), 4.76 (2H, d, J=5.6Hz), 4.8–5.1 (5H, m), 5.09 (1H, d, J=5.5Hz), 5.16 (1H, d, J=3.1Hz), 5.23 (1H, d, J=5.5Hz), 5.51 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.2Hz), 6.8–6.9 (2H, m), 7.0–7.1 (3H, m), 7.3–7.5 (3H, m), 7.67 (2H, d, J=6.9Hz), 7.71 (2H, d, J=6.9Hz), 7.95 (2H, d, J=8.4Hz), 8.05 (1H, d, J=7.0Hz), 8.23 (1H, d, J=7.7Hz), 8.70 (1H, d, J=7.0Hz), 8.84 (1H, s)

FAB-MASS: m/z=1377.1 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{60}H_{83}N_8O_{24}NaS.5H_2O$: C 49.86, H 6.49, N 7.75 Found: C 49.74, H 6.73, N 7.68

EXAMPLE 104

IR (KBr): 3349, 2937, 2858, 1672, 1629, 1537, 1444, 1249, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.6Hz), 1.2–1.7 (14H, m), 1.7–2.1 (5H, m), 2.1–2.4 (5H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.4–3.6 (4H, m), 3.7–4.5 (16H, m), 4.77 (2H, d, J=5.7Hz), 4.8–5.2 (5H, m), 5.09 (1H, d, J=5.6Hz), 5.16 (1H, d, J=3.1Hz), 5.24 (1H, d, J=4.5Hz), 5.51 (1H, d, J=5.8Hz), 6.73 (1H, d, J=8.2Hz), 6.8–6.9 (2H, m), 7.0–7.1 (3H, m), 7.3–7.5 (3H, m), 7.6–7.8 (4H, m), 7.96 (2H, d, J=8.4Hz), 8.10 (1H, d, J=8.4Hz), 8.24 (1H, d, J=7.7Hz), 8.71 (1H, d, J=7.0Hz), 8.89 (1H, s)

FAB-MASS: m/z=1386.5 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{61}H_{82}N_9O_{23}NaS.6H_2O$: C 49.76, H 6.43, N 8.56 Found: C 49.99, H 6.39, N 8.52

EXAMPLE 105

IR (KBr): 3350, 2933, 2856, 1664, 1631, 1604, 1511, 1450, 1243, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.5Hz), 1.05 (3H, d, J=5.7Hz), 1.2–1.5 (8H, m), 1.6–2.0 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.0–3.3 (5H, m),

3.6–4.4 (20H, m), 4.7–5.1 (7H, m), 5.10 (1H, d, J=5.5Hz), 5.16 (1H, d, J=3.1Hz), 5.27 (1H, d, J=4.5Hz), 5.51 (1H, d, J=6.0Hz), 6.7–7.1 (9H, m), 7.2–7.5 (3H, m), 8.0–8.2 (2H, m), 8.2–8.4 (1H, m), 8.4–8.6 (1H, m), 8.66 (1H, d, J=2.2Hz), 8.85 (1H, s)

FAB-MASS: m/z=1360 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{58}H_{80}N_{11}O_{22}SNa.6H_2O$: C 48.16, H 6.41, N 10.65 Found: C 47.91, H 6.31, N 10.56

EXAMPLE 106

IR (KBr): 3369, 3345, 2935, 1672, 1629, 1511, 1245, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7Hz), 1.06 (3H, d, J=5.8Hz), 1.3–1.6 (10H, m), 1.6–2.0 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.20 (3H, s), 3.28 (2H, t, J=6.4Hz), 3.1–3.4 (5H, m), 3.7–4.5 (20H, m), 4.7–5.1 (7H, m), 5.08 (1H, d, J=5.5Hz), 5.15 (1H, d, J=3.1Hz), 5.23 (1H, d, J=4.5Hz), 5.48 (1H, d, J=5.8Hz), 6.73 (1H, d, J=8.2Hz), 6.82 (2H, d, J=9.1Hz), 6.94 (2H, d, J=9.1Hz), 6.9–7.0 (1H, m), 7.04 (1H, s), 7.3–7.5 (3H, m), 8.0–8.1 (2H, m), 8.27 (1H, d, J=7.7Hz), 8.49 (1H, d, J=7.0Hz), 8.66 (1H, d, J=2.2Hz), 8.84 (1H, s)

FAB-MASS: m/z=1404 ($M+Na^+$)

EXAMPLE 107

IR (KBr): 3357, 1647, 1631, 1537, 1444, 1249, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.1 (6H, m), 1.09 (3H, d, J=5.9Hz), 1.6–2.4 (8H, m), 2.4–2.5 (1H, m), 3.1–3.3 (1H, m), 3.6–4.5 (16H, m), 4.8–5.2 (7H, m), 5.10 (1H, d, J=5.6Hz), 5.17 (1H, d, J=3.1Hz), 5.25 (1H, d, J=4.5Hz), 5.55 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.2Hz), 6.8–7.0 (2H, m), 7.0–7.6 (6H, m), 7.73 (2H, d, J=8.7Hz), 7.86 (2H, d, J=8.5Hz), 8.0–8.3 (8H, m), 8.84 (1H, s), 8.9–9.0 (1H, m)

FAB-MASS: m/z=1379.4 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{59}H_{69}N_{10}O_{22}S_2Na.6H_2O$: C 48.36, H 5.57, N 9.56 Found: C 48.18, H 5.60, N 9.36

The Object Compounds (108) to (117) were obtained according to a similar manner to that of Example 27.

EXAMPLE 108

IR (KBr): 3350, 2933, 1670, 1627, 1521, 1436, 1272, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7Hz), 0.92 (3H, d, J=6.7Hz), 1.1–1.4 (11H, m), 1.7–2.4 (9H, m), 3.1–3.2 (1H, m), 3.5–5.4 (27H, m), 6.6–7.2 (8H, m), 7.5–7.8 (3H, m), 7.8–8.0 (3H, m), 8.1–8.8 (3H, m)

FAB-MASS: m/z=1249.4 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{52}H_{71}N_{10}O_{21}NaS.7H_2O$: C 46.15, H 6.33, N 10.35 Found: C 46.12, H 6.35, N 10.24

EXAMPLE 109

IR (Kbr pelet): 3361, 2933, 2856, 1670, 1652, 1616, 1540, 1508, 1448, 1261, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, d, J=6.6Hz), 0.97 (3H, d, J=6.8Hz), 1.12 (3H, d, J=6.8Hz), 1.2–1.5 (10H, m), 1.7–2.0 (5H, m), 2.2–2.6 (4H, m), 3.1–3.2 (1H, m), 3.7–4.4 (16H, m), 4.8–5.3 (10H, m), 5.59 (1H, d, J=6.0Hz), 6.7–6.9 (3H, m), 7.0–7.4 (7H, m), 7.8–8.2 (4H, m), 8.8–9.0 (2H, m)

FAB-MASS: m/z=1280.3 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{54}H_{72}N_9O_{23}NaS.7H_2O$: C 46.45, H 6.21, N 9.03 Found: C 46.68, H 6.44, N 9.03

EXAMPLE 110

IR (KBr): 3350, 2931, 1670, 1627, 1540, 1436, 1276, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.8Hz), 0.93 (2H, d, J=8.8Hz), 1.08 (2H, d, J=5.9Hz), 1.2–1.4 (4H, m), 1.5–1.7 (2H, m), 1.7–2.1 (3H, m), 2.1–2.4 (3H, m), 2.6–2.7 (3H, m), 3.1–3.3 (1H, m), 3.6–4.5 (17H, m), 4.7–5.4 (8H, m), 6.73 (1H, d, J=8.2Hz), 6.83 (2H, d, J=8.2Hz, 7.0–7.1 (1H, m), 7.2–7.5 (5H, m), 7.65 (2H, d, J=8.2Hz), 7.74 (2H, d, J=8.4Hz), 7.98 (2H, d, J=8.4Hz), 8.08 (1H, d, J=8.5Hz), 8.25 (1H, d, J=8.5Hz), 8.74 (1H, d, J=7.6Hz), 8.7–9.0 (1H, br)

FAB-MASS: m/z=1231.2 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{53}H_{69}N_8O_{21}NaS.3H_2O$: C 50.39, H 5.98, N 8.87 Found: C 50.34, H 6.25, N 8.90

EXAMPLE 111

IR (KBr): 3353.6, 1670.1, 1652.7, 1623.8 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7Hz), 1.07 (3H, d, J=5.6Hz), 1.0–1.62 (8H, m), 1.62–2.00 (5H, m), 2.10–2.65 (4H, m), 3.20 (3H, s), 3.08–3.40 (1H, m), 3.30 (2H, t, J=6.5Hz), 3.53–4.50 (15H, m), 4.68–5.13 (9H, m), 5.16 (1H, d, J=2.9Hz), 5.26 (1H, d, J=4.5Hz), 5.53 (1H, d, J=5.9Hz), 6.68–6.95 (4H, m), 6.95–7.11 (3H, m), 7.20–7.52 (3H, m), 7.55–7.95 (7H, m), 8.13 (1H, d, J=8.4Hz), 8.31 (1H, d, J=7.7Hz), 8.53 (1H, d, J=7.0Hz), 8.85 (1H, s)

FAB-MASS: m/z=1331.5 (M+Na–1)

Elemental Analysis Calcd. for $C_{58}H_{77}N_8NaO_{23}S.6H_2O$: C 49.15, H 6.33, N 7.91 Found: C 49.07, H 6.53, N 7.84

EXAMPLE 112

IR (KBr): 3350, 2937, 1673, 1646, 1631, 1538, 1519, 1456, 1247, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.6Hz), 1.07 (3H, d, J=5.7Hz), 1.3–2.4 (25H, m), 2.5–2.6 (1H, m), 3.2–3.4 (1H, m), 3.5–4.6 (20H, m), 4.8–5.7 (11H, m), 6.73 (1H, d, J=8.0Hz), 6.9–7.0 (2H, m), 7.0–7.2 (3H, m), 7.3–7.6 (3H, m), 7.74 (2H, d, J=8.5Hz), 7.77 (2H, d, J=8.3Hz), 8.02 (2H, d, J=8.3Hz), 8.13 (1H, d, J=8.4Hz), 8.30 (1H, d, J=7.7Hz), 8.77 (1H, d, J=7.0Hz), 8.85 (1H, s)

FAB-MASS: m/z=1389 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{61}H_{83}N_8O_{24}NaS.7H_2O$: C 49.06, H 6.55, N 7.50 Found: C 49.03, H 6.54, N 7.56

EXAMPLE 113

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.7Hz), 1.07 (3H, d, J=5.9Hz), 1.1–1.3 (14H, m), 1.7–2.1 (5H, m), 2.2–2.5 (3H, m), 2.6–2.7 (1H, m), 3.1–3.3 (1H, m), 3.7–4.5 (16H, m), 4.7–5.1 (7H, m), 5.10 (1H, d, J=5.5Hz), 5.16 (1H, d, J=3.1Hz), 5.25 (1H, d, J=4.5Hz), 5.49 (1H, d, J=5.7Hz), 6.53 (1H, d, J=3.1Hz), 6.73 (1H, d, J=8.2Hz), 6.8–6.9 (2H, m), 7.05 (1H, m), 7.31 (1H, d, J=8.1Hz), 7.4–7.6 (4H, m), 7.70 (1H, d, J=6.7Hz), 8.08 (1H, d, J=8.4Hz), 8.18 (1H, s), 8.31 (1H, d, J=7.7Hz), 8.57 (1H, d, J=7.0Hz), 8.85 (1H, s)

FAB-MASS: m/z=1264 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{54}H_{76}N_9O_{21}NaS.6H_2O$: C 48.03, H 6.57, N 9.34 Found: C 48.02, H 6.61, N 9.28

EXAMPLE 114

IR (KBr): 3350, 2937, 1668, 1631, 1537, 1247, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=7.4Hz), 0.96 (3H, d, J=6.5Hz), 1.07 (3H, d, J=5.7Hz), 1.3–1.7 (7H, m), 1.7–2.1

(5H, m), 2.2–2.4 (3H, m), 2.6–2.7 (1H, m), 3.0–3.8 (16H, m), 3.8–4.6 (11H, m), 4.7–5.3 (6H, m), 6.73 (1H, d, J=8.2Hz), 6.8–7.0 (2H, m), 7.0–7.2 (3H, m), 7.3–7.5 (3H, m), 7.6–7.8 (4H, m), 7.96 (2H, d, J=8.3Hz), 8.11 (1H, d, J=8.2Hz), 8.26 (1H, d, J=7.6Hz), 8.6–9.0 (2H, m)

FAB-MASS: m/z=1319.4 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{57}H_{77}N_8O_{23}NaS.8H_2O$: C 47.50, H 6.50, N 7.77 Found: C 47.72, H 6.85, N 7.85

EXAMPLE 115

IR (KBr): 3350, 1666, 1631, 1546, 1276, 1247 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=7.5Hz), 1.08 (3H, d, J=5.7Hz), 1.4–1.6 (4H, m), 1.6–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.23 (3H, s), 3.3–3.5 (2H, m), 3.7–4.5 (16H, m), 4.79 (2H, d, J=6.2Hz), 4.8–5.1 (5H, m), 5.11 (1H, d, J=5.6Hz), 5.18 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.4Hz), 5.54 (1H, d, J=5.7Hz), 6.73 (1H, d, J=8.1Hz), 6.8–7.0 (2H, m), 7.0–7.1 (3H, m), 7.3–7.5 (3H, m), 7.6–7.9 (8H, m), 8.01 (2H, d, J=8.4Hz), 8.08 (1H, d, J=8.4Hz), 8.32 (1H, d, J=7.7Hz), 8.80 (1H, d, J=7.0Hz), 8.85 (1H, s)

FAB-MASS: m/z=1353.9 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{60}H_{75}N_8O_{23}NaS.9.5H_2O$: C 47.96, H 6.31, N 7.46 Found: C 47.97, H 6.25, N 7.41

EXAMPLE 116

IR (KBr): 3450, 2935, 1675, 1650, 1540, 1513, 1454, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.9Hz), 1.60 (6H, s), 1.7–2.4 (6H, m), 2.5–2.6 (1H, m), 3.1–3.6 (5H, m), 3.7–4.5 (14H, m), 4.7–5.0 (3H, m), 5.0–5.2 (4H, m), 5.11 (1H, d, J=5.5Hz), 5.18 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.5Hz), 5.56 (1H, d, J=6.0Hz), 6.8–7.5 (9H, m), 7.84 (2H, d, J=8.8Hz), 8.0–8.4 (6H, m), 8.85 (1H, s), 8.91 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1328 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{55}H_{68}N_{11}O_{21}S_2Na.8H_2O$: C 45.55, H 5.84, N 10.62 Found: C 45.62, H 5.70, N 10.54

EXAMPLE 117

IR (KBr): 3350, 2939, 1664, 1627, 1531, 1446, 1249, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.8–1.0 (6H, m), 1.4–1.9 (9H, m), 2.0–2.5 (4H, m), 3.1–3.2 (1H, m), 3.22 (3H, s), 3.3–3.4 (2H, m), 3.51 (2H, s), 3.6–4.4 (16H, m), 4.7–5.2 (7H, m), 5.07 (1H, d, J=5.6Hz), 5.17 (1H, d, J=3.1Hz), 5.23 (1H, d, J=4.5Hz), 5.54 (1H, d, J=5.9Hz), 6.7–6.8 (3H, m), 7.0–7.4 (8H, m), 7.5–7.7 (4H, m), 7.70 (4H, s), 8.1–8.2 (2H, m), 8.51 (1H, d, J=7.0Hz), 8.83 (1H, s)

FAB-MASS: m/z=1367.6 (*M+Na*$^+$)

Elemental Analysis Calcd. for $C_{61}H_{77}N_8O_{23}SNa.6.5H_2O$: C 50.01, H 6.20, N 7.66 Found: C 50,30, H 6.50, N 7.75

EXAMPLE 118

To a solution of The Object Compound (61) (0.25 g) in methanol (50 ml) was added dry 10% palladium on carbon (0.2 g) and stirred for 6 hours under hydrogen atmosphere. The palladium on carbon was filtered off, and the filtrate was evaporated under reduced pressure to give Object Compound 118 (179 mg).

IR (KBr): 3400, 1668.1, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.92 (3H, d, J=6.7Hz), 1.1–2.45 (40H, m), 3.20 (3H, s), 3.28 (2H, t, J=6.5Hz), 3.0–3.4 (1H, m), 3.5–4.7 (14H, m), 4.95–5.5 (12H, m), 6.55 (1H, d, J=8.4Hz), 6.84 (1H, s), 6.86 (1H, d, J=8.4Hz), 7.0–7.3 (4H, m), 7.9–8.3 (4H, m)

FAB-MASS: m/z=1292 (M+Na)

Elemental Analysis Calcd. for $C_{54}H_{88}N_9O_{22}SNa.5H_2O$: C 47.67, H 7.26, N 9.26 Found: C 47.72, H 7.35, N 8.95

The Object Compounds (119) to (121) were obtained according to a similar manner to that of Example 118.

EXAMPLE 119

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.6Hz), 1.00 (3H, d, J=7.3Hz), 1.03 (3H, d, J=6.0Hz), 1.2–1.5 (4H, m), 1.5–2.0 (5H, m), 2.1–2.7 (8H, m), 3.17 (1H, m), 3.6–4.5 (14H, m), 4.65–5.7 (12H, m), 6.72 (1H, d, J=8.1Hz), 6.75 (1H, s), 6.80 (1H, d, J=8.1Hz), 7.05 (1H, s), 7.1–7.7 (15H, m), 8.0–8.6 (4H, m), 8.85 (1H, s)

FAB-MASS: m/z=1274 (M+Na)

Elemental Analysis Calcd. for $C_{55}H_{74}N_9O_{21}SNa.7H_2O$: C 47.93, N 6.43, N 9.15 Found: C 48.12, N 6.56, N 9.03

EXAMPLE 120

IR (KBr): 3355.5, 1672.0 1629.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6Hz), 0.98 (3H, d, J=6.5Hz), 1.03 (3H, d, J=6.0Hz), 1.2–2.6 (21H, m), 3.18 (1H, m), 3.6–4.5 (16H, m), 4.65–5.55 (12H, m), 6.6–7.5 (10H, m), 8.0–8.6 (4H, m), 8.89 (1H, s) FAB-MASS: m/z=1256 (M+Na)

EXAMPLE 121

IR (KBr): 3357.5, 1660.4, 1629.6, 1249.6 $cm^{31\ 1}$

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6Hz), 0.96 (3H, d, J=6.8Hz), 1.03 (3H, d, J=6.0Hz), 1.1–1.5 (12H, m), 1.6–2.0 (5H, m), 2.0–2.5 (4H, m), 3.07 (1H, m), 3.5–4.5 (16H, m), 4.6–5.6 (12H, m), 6.72 (1H, d, J=8.1Hz), 6.7–6.9 (4H, m), 7.04 (1H, s), 7.16 (1H, s), 7.1–7.5 (2H, m), 7.25 (2H, d, J=8.6Hz), 8.0–8.2 (3H, m), 8.46 (1H, d, J=7Hz), 8.84 (1H, s)

FAB-MASS: m/z=1256 (M+Na)

Elemental Analysis Calcd. for $C_{52}H_{76}N_9O_{22}SNa.7H_2O$: C 45.91, H 6.67, N 9.27 Found: C 45.98, H 6.67, N 9.10

EXAMPLE 122

A solution of Object Compound (11) (795 mg) in water (16 ml) was left for 240 hours. The solution was subjected to column chromatography on ODS (YMC-gel ODS-AMS50) and eluted with 25% CH_3CN/H_2O. The fractions containing Object Compound were combined and the acetonitrile was removed under reduced pressure. The residue was lyophilized to give Object Compound (123) (38 mg).

IR (KBr): 3361, 2956, 2875, 1668, 1627, 1521, 1249, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.8–1.5 (19H, m), 1.6–2.4 (13H, m), 3.1–3.2 (1H, m), 3.5–4.1 (12H, m), 4.1–4.7 (10H, m), 4.9–5.6 (5H, m), 5.98 (1H, d, J=10.6Hz), 6.36 (1H, d, J=10.6Hz), 6.7–7.3 (12H, m), 7.4–8.0 (7H, m)

FAB-MASS: m/z=1273.1 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{22}NaS.11H_2O$: C 45.58, H 6.47, N 7.73 Found: C 45.83, H 6.26, N 7.75

The Object Compound (123) was obtained according to a similar manner to that of Example 118.

EXAMPLE 123

IR (KBr): 3349.7, 1670.1, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=7.2Hz), 0.96 (3H, d, J=6.7Hz), 1.13 (3H, d, J=5.7Hz), 1.18–1.55 (10H, m), 1.58–2.08 (5H, m), 2.08–2.90 (4H, m), 2.90–3.30 (2H, m), 3.60–4.50 (17H, m), 4.70–5.70 (12H, m), 6.65–7.60 (11H, m), 7.80 (2H, br s), 7.95–8.23 (2H, m), 8.75 (1H, d, J=7.0Hz), 8.85 (1H, s)

FAB-MASS: m/z=1114.4 ($M-SO_4-2$)

Elemental Analysis Calcd. for $C_{52}H_{77}N_9O_{21}S.6H_2O$: C 47.88, H 6.88, N 9.66 Found: C 47.60, H 6.74, N 9.53

The following compound (124) was obtained according to a similar manner to that of Example 1.

EXAMPLE 124

IR (KBr): 3324, 2937, 2873, 1664, 1629, 1442, 1257 cm^{-1}

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.1Hz), 0.96 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.7Hz), 1.3–1.5 (4H, m), 1.7–2.6 (9H, m), 3.1–3.3 (1H, m), 3.7–4.6 (16H, m), 4.7–5.1 (7H, m), 5.11 (1H, d, J=5.6Hz), 5.17 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.5Hz), 5.55 (1H, d, J=5.8Hz), 6.7–6.9 (3H, m), 7.0–7.6 (6H, m), 7.97 (2H, d, J=8.8Hz), 8.0–8.4 (6H, m), 8.85 (1H, s), 8.92 (1H, d, J=7.0Hz)

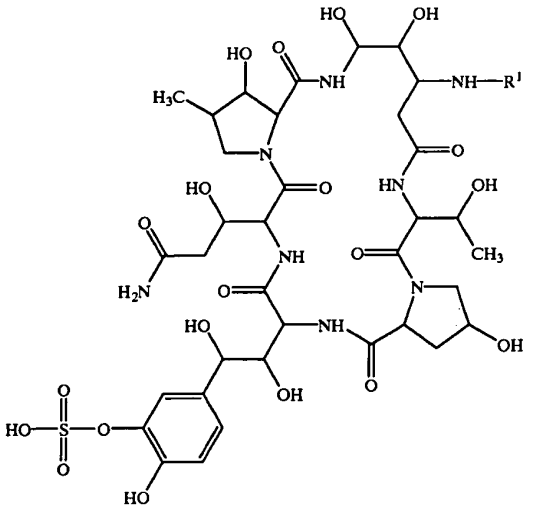
FAB-MASS: m/z=1331 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{55}H_{69}N_{10}O_{22}NaS_2$: C 45.45, H 5.89, N 9.64 Found: C 45.71, H 5.68, N 9.60

What is claimed is:

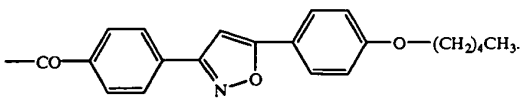
1. A polypeptide compound of the following general formula (I):

(I)



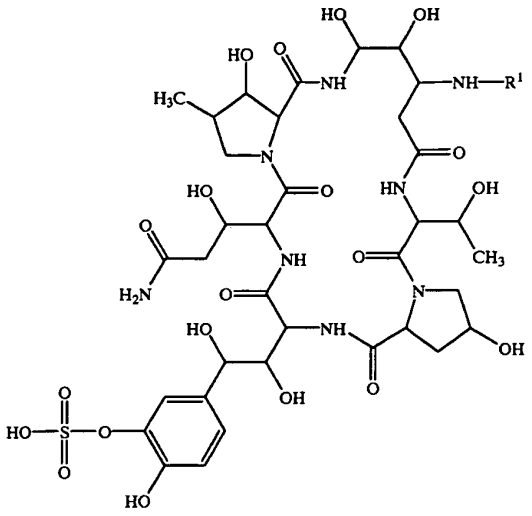
wherein R^1 is benzoyl substituted with isoxazolyl which has phenyl having lower alkoxy, or a salt thereof.

2. A compound of claim 1, wherein R^1 is



3. A process for the preparation of a polypeptide compound of the formula (I):

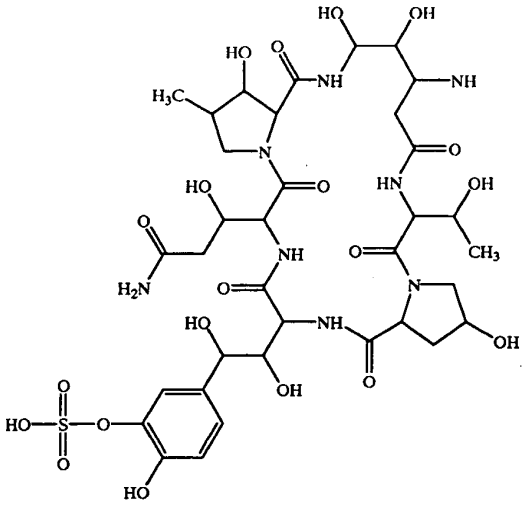
(I)



wherein R^1 is benzoyl substituted with isoxazolyl which has phenyl having lower alkoxy, or a salt thereof, said process comprising:

1) reacting a compound of the formula (II):

(II)



or its reactive derivative at the amino group or a salt thereof, with a compound of formula (III):

R^1—OH (III)

or its reactive derivative at the carboxy group or a salt thereof, wherein R^1 is defined above, to give a compound of formula (I).

4. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1, or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or excipient.

5. A method for the therapeutic treatment of infectious diseases caused by pathogenic microorganisms, comprising administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, to a human being or animal.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,107,458

DATED : August 22, 2000

INVENTOR(S): Hidenori OHKI et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page, item [30], the Foreign Application Priority Data is erroneously listed. It should be:

--[30] Foreign Application Priority Data

Oct. 7, 1994 [GB] United Kingdom.....9420425
Apr. 28, 1995 [GB] United Kingdom.....9508745--

Signed and Sealed this

Twenty-ninth Day of May, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office