

JAN 13 2004

PTO/SB/17 (10-03)

Approved for use through 7/31/2006. OMB 0651-0032

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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<h2 style="text-align: center;">FEE TRANSMITTAL for FY 2004</h2> <p style="text-align: center; font-size: small;">Effective 10/01/2003, Patent fees are subject to annual revision.</p>		Complete if Known		
		Patent Number	5,859,006	
		Issue Date	January 12, 1999	
		First Named Inventor	Daugan	
		Examiner Name	N/A	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27		Art Unit	N/A	
TOTAL AMOUNT OF PAYMENT	(\$)	1,120.00	Attorney Docket No.	29342/33751

METHOD OF PAYMENT (check all that apply)		FEE CALCULATION (continued)																																																																																																																																																																																																	
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<input checked="" type="checkbox"/> Deposit Account: Deposit Account Number: 13-2855 Deposit Account Name: MARSHALL, GERSTEIN & BORUN LLP		<table border="1"> <thead> <tr> <th colspan="2">Large Entity</th> <th colspan="2">Small Entity</th> <th rowspan="2">Fee Description</th> <th rowspan="2">Fee Paid</th> </tr> <tr> <th>Fee Code</th> <th>Fee (\$)</th> <th>Fee Code</th> <th>Fee (\$)</th> </tr> </thead> <tbody> <tr> <td>1051</td> <td>130</td> <td>2051</td> <td>65</td> <td>Surcharge - late filing fee or oath</td> <td></td> </tr> <tr> <td>1052</td> <td>50</td> <td>2052</td> <td>25</td> <td>Surcharge - late provisional filing fee or cover sheet.</td> <td></td> </tr> <tr> <td>1053</td> <td>130</td> <td>1053</td> <td>130</td> <td>Non-English specification</td> <td></td> </tr> <tr> <td>1812</td> <td>2,520</td> <td>1812</td> <td>2,520</td> <td>For filing a request for <i>ex parte</i> reexamination</td> <td></td> </tr> <tr> <td>1804</td> <td>920*</td> <td>1804</td> <td>920*</td> <td>Requesting publication of SIR prior to Examiner action</td> <td></td> </tr> <tr> <td>1805</td> <td>1,840*</td> <td>1805</td> <td>1,840*</td> <td>Requesting publication of SIR after Examiner action</td> <td></td> </tr> <tr> <td>1251</td> <td>110</td> <td>2251</td> <td>55</td> <td>Extension for reply within first month</td> <td></td> </tr> <tr> <td>1252</td> <td>420</td> <td>2252</td> <td>210</td> <td>Extension for reply within second month</td> <td></td> </tr> <tr> <td>1253</td> <td>950</td> <td>2253</td> <td>475</td> <td>Extension for reply within third month</td> <td></td> </tr> <tr> <td>1254</td> <td>1,480</td> <td>2254</td> <td>740</td> <td>Extension for reply within fourth month</td> <td></td> </tr> <tr> <td>1255</td> <td>2,010</td> <td>2255</td> <td>1,005</td> <td>Extension for reply within fifth month</td> <td></td> </tr> <tr> <td>1401</td> <td>330</td> <td>2401</td> <td>165</td> <td>Notice of Appeal</td> <td></td> </tr> <tr> <td>1402</td> <td>330</td> <td>2402</td> <td>165</td> <td>Filing a brief in support of an appeal</td> <td></td> </tr> <tr> <td>1403</td> <td>290</td> <td>2403</td> <td>145</td> <td>Request for oral hearing</td> <td></td> </tr> <tr> <td>1451</td> <td>1,510</td> <td>1451</td> <td>1,510</td> <td>Petition to institute a public use proceeding</td> <td></td> </tr> <tr> <td>1452</td> <td>110</td> <td>2452</td> <td>55</td> <td>Petition to revive - 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SUBMITTED BY		(Complete if applicable)	
Name (Print/Type)	James J. Napoli	Registration No. (Attorney/Agent)	32,361
Telephone	(312) 474-6614	Date	January 9, 2004
Signature	<i>James J. Napoli</i>		

2004E-0413

APP 1

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:)
)
ALAIN CLAUDE-MARIE DAUGAN)
)
U.S. Patent No. 5,589,006)
)
Issue Date: January 12, 1999)
)
For: **TETRACYCLIC DERIVATIVES,**)
PROCESS OF PREPARATION AND USE)
)
Assignee: ICOS Corporation)
)
Attorney Docket No. 27866/33751)
)

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

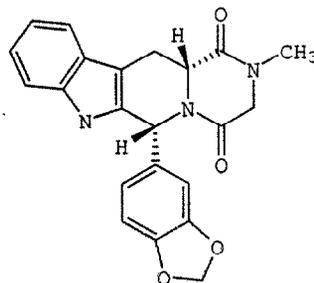
Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. §156, ICOS Corporation, owner of the above-identified patent by an Assignment recorded on July 14, 1997, on Reel 8610, Frame 428, hereby requests an extension of the patent term of U.S. Patent No. 5,859,006. The following information is submitted in accordance with 35 U.S.C. 156(d) and 37 C.F.R. 1.710 et seq. and follows the numerical format set forth in 37 C.F.R. §1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is tadalafil which has the chemical name (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione and has the following structure:



Tadalafil alternatively has the chemical name pyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl, (6R,12aR)-. Tadalafil is the active ingredient in the product CIALIS® as may be seen from attached Exhibit A, which is the Product Information sheet for this product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. §301 et seq. Section 505 provides for the

submission and approval of new drug applications (NDAs) for human drug products meeting the definition of "new drug" under Section 201(p) of the Act.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Tadalafil was approved by the Food and Drug Administration (FDA) for commercial marketing pursuant to Section 505 of the FDCA on November 21, 2003.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it 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, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

As stated in Sections 1, 2, and 3 above, the active ingredient in the product CIALIS® is tadalafil. Tadalafil had not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act until November 21, 2003.

(5) A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted:

The product was approved on November 21, 2003 and the last day within the sixty-day period permitted for submission of an application for extension of a

patent is January 20, 2004. As evident from the Certificate of Mailing by "Express Mail" pursuant to 37 C.F.R. 1.10, this application is timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

Inventor: Alain Claude-Marie Daugan
U.S. Patent No. 5,859,006
Issue Date: January 12, 1999
Expiration Date: January 12, 2016

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings:

A copy of the patent is attached as Exhibit B.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:

A copy of a Certificate of Correction issued by the U.S. Patent Office on September 28, 1999 is attached as Exhibit C. A copy of a Request for Certificate of Correction Under Rules 322(a) and 323, mailed to the U.S. Patent Office on December 17, 2003, is attached as Exhibit D.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

The patent claims the approved product, which is (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione. Claims 1-4, 6-8, and 10-13 of the patent claim tadalafil. The approved product is in the form of a free base, which is identified at column 36, lines 50-67 continuing to column 37, lines 1-14. Thus, the approved product is specifically embraced by claim 13 of the patent. Claim 13 of the patent claims (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, which is the approved product. Accordingly, claims 1-4, 6-8, and 10-13 all read on the approved product.

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

(ii) For a patent claiming a new animal drug, the date a major health or environmental effects test on the drug was initiated and any available sub-

stantiation of that date or the date of an exemption under subsection (j) of section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug; the date on which a new animal drug application (NADA) was initially submitted and the NADA number; and the date on which the NADA was approved;

(iii) For a patent claiming a veterinary biological product, the date the authority to prepare an experimental biological product under the Virus-Serum-Toxin Act became effective; the date an application for a license was submitted under the Virus-Serum-Toxin Act; and the date the license issued;

(iv) For a patent claiming a food or color additive, the date a major health or environmental effects test on the additive was initiated and any available substantiation of that date; the date on which a petition for product approval under the Federal Food, Drug, and Cosmetic Act was initially submitted and the petition number; and the date on which the FDA published the Federal Register notice listing the additive for use;

(v) For a patent claiming a medical device, the effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device if no IDE was submitted and any available substantiation of that date; the date on which the application for product approval or notice of completion of a product development protocol under section 515 of the Federal Food, Drug, and Cosmetic Act was initially submitted and the number of the application or protocol; and the date on which the application was approved or the protocol declared to be completed:

On November 6, 1997, ICOS Corporation, the assignee of U.S. Patent No. 5,859,006, submitted to the FDA a "Notice of Claimed Investigational Exemption for a New Drug" (IND) under Section 505(i) of the FDCA to permit the interstate shipment of tadalafil for the purpose of conducting clinical studies to support the approval of a subsequent NDA for tadalafil. A copy of the letter transmitting the IND to the FDA is attached as Exhibit E. By letter dated November 17, 1997, the FDA acknowledged receipt of the IND, assigned the IND number 54,553, and indicated that the IND would become effective thirty days after the date of its receipt on December 10, 1997. A copy of this letter is attached as Exhibit F. The IND was placed on hold prior to the end of the thirty-day period and was released from hold to proceed with U.S. clinical studies in a letter dated July 29, 1998. A copy of this letter is attached as Exhibit G. This establishes the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(1) as July 29, 1998, the effective date of an exemption under Section 505(i).

Lilly ICOS LLC submitted an NDA for tadalafil, NDA 21-368, on June 28, 2001. A copy of the letter transmitting the NDA is attached as Exhibit H. The NDA submission was received by the FDA on June 29, 2001 as indicated by Exhibit I. Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), June 29, 2001 is the date of initial submission of a new drug application under Section 505 for tadalafil.

The NDA described above was approved on November 21, 2003. Attached as Exhibit J is a letter

dated November 21, 2003 from the FDA to Lilly ICOS LLC approving the NDA for tadalafil. Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), November 21, 2003 is the date of approval of the application for tadalafil submitted on June 28, 2001.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

During the applicable regulatory review period, Lilly ICOS LLC was actively involved in obtaining NDA approval for tadalafil. As discussed in paragraph (10) above, the IND for tadalafil was submitted on November 6, 1997, the NDA was submitted on June 28, 2001, and the NDA was approved on November 21, 2003. Lilly ICOS LLC was in close consultation with the FDA during the clinical studies conducted under the IND. Similarly, subsequent to the submission of the NDA, Lilly ICOS LLC had numerous contacts and meetings with the FDA with respect to the approval and, in fact, conducted additional studies at FDA's request to support the NDA approval. The description of significant activities undertaken by Lilly ICOS LLC with respect to tadalafil during the regulatory review period as set forth in Exhibit K is illustrative of the activities involved. Because Applicant is claiming less than a two (2) year extension, only very basic information regarding activities during the IND period is presented here but more detailed information regarding this period would be available upon request from the Commissioner or Secretary.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) The term of U.S. Patent No. 5,859,006 expires on January 12, 2016. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This application is submitted by the owner of record, ICOS Corporation (Assignment recorded on July 14, 1997, on Reel 8610, Frame 428). A copy of this assignment is attached as Exhibit L. This application is submitted in accordance with 35 U.S.C. 156(d) in that it is submitted within the sixty-day period

beginning on the date, November 21, 2003, the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. 156(d).

(4) As evidenced by the November 21, 2003 letter from the FDA (Exhibit J), the product was subject to a regulatory review period under Section 505 of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of tadalafil after regulatory review under Section 505 is the first permitted commercial marketing of tadalafil.

This is confirmed by the absence of any approved new drug application for tadalafil prior to November 21, 2003.

(b) Statement as to length of extension claimed:

The term of U.S. Patent No. 5,859,006 should be extended by 679 days to November 21, 2017. This extension was determined on the following basis: as set forth in 35 U.S.C. §156(g)(1) and 37 C.F.R. §1.775(c), the regulatory review period equals the length of time between the effective date of the initial IND July 29, 1998, and the initial submission of the NDA June 29, 2001, a period of 1,066 days, plus the length of time between the initial submission of the NDA June 29, 2001 to NDA approval November 21, 2003, a period of 875 days. These two periods added together equal 1941 days.

Pursuant to 35 U.S.C. §156(c) and 37 C.F.R. §1.775 (d)(1)(i), the term of the patent eligible for

extension shall be extended by the time equal to the regulatory review period which occurs after the date the patent was issued. In this case, this is a period running from the date of patent issue, January 12, 1999, to the date of NDA approval, November 21, 2003, a period of 1,774 days.

As discussed in paragraph (11) above and as illustrated in Exhibit K, Lilly ICOS LLC was continuously and diligently working toward securing NDA approval for tadalafil. As Lilly ICOS LLC acted with due diligence during the entire period of regulatory review, the 1,774-day period calculated above as the term of the patent eligible for extension should not be reduced for lack of diligence under 35 U.S.C. 156(c)(1) or 37 C.F.R. 1.775 (d)(1)(ii).

Pursuant to 35 U.S.C. §156(c)(2) and 37 C.F.R. §1.775 (d)(1)(iii), this 1,774-day period is to be reduced by one-half of the time from the effective date of the initial IND July 29, 1998, or the date of patent issue, January 12, 1999, whichever is later, to the date of initial submission of the NDA, June 29, 2001, a period of 899 days. One-half of this period is 449 days. Thus, the 1,774-day period is reduced by 449 days leaving a revised regulatory period of 1,325 days.

Pursuant to 35 U.S.C. §156(c)(3) and 37 C.F.R. §1.775(d)(2-4), if the period remaining in the term of the patent after the date of approval November 21, 2003 to January 12, 2016, a period of 4,435 days, when added to the revised regulatory review period (1,325 days) exceeds 14 years (5,113 days), the period of extension must be reduced so that the total of both such periods does not exceed fourteen years. In this

case, the total of both such periods exceeds 14 years by 647 days. Therefore, the 1,325-day revised regulatory review period must be reduced by 647 days to a 679-day period.

The period of patent term extension as calculated above is also subject to the provisions of 35 U.S.C. 156(g)(4) and 37 C.F.R. 1.775(d)(5-6). The patent to be extended issued after clinical evaluation of the approved product began after the enactment of the statute, September 24, 1984. Since commercial marketing of the drug was approved after enactment of the statute, the five-year maximum on extension as provided in 35 U.S.C. §156(g)(6)[(A)][(B)][(C)] and 37 C.F.R. §1.775(d)[(5)][(6)] is applicable. Since this maximum is greater than the period calculated above, the term of the patent is eligible for a 679-day extension until November 21, 2017.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner for Patents 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 (See §1.765):

Applicant acknowledges a duty to disclose to the Commissioner for Patents and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought. Applicant is unaware of any such information other than that already presented in this application and attached exhibits.

(14) The prescribed fee for receiving and acting upon the application for extension (see §1.20(j)):

As indicated by the letter of transmittal submitted with this application, the Commissioner for Patents has been authorized to charge the filing fee of \$1,120.00 and any additional fees which may be required by this or any other related paper, or credit any overpayment to Deposit Account No. 13-2855 in the name of Marshall, Gerstein and Borun and any additional fees which may be required.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Address all correspondence to James J. Napoli, Marshall, Gerstein & Borun, 233 South Wacker Drive, Chicago, Illinois 60606.

Direct telephone calls to James J. Napoli at (312)474-6300.

(16) A duplicate of the application papers, certified as such:

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. §156, including its attachments and supporting papers, is being submitted with a duplicate copy thereof.

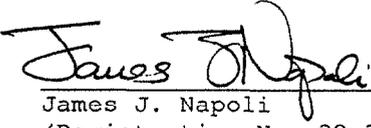
(17) An oath or declaration as set forth in [37 C.F.R. 1.740(b)]:

As the undersigned agent of ICOS Corporation, the owner of record of U.S. Patent No. 5,859,006, which, by submission of this paper and attached Exhibits, now applies for an extension of term of this patent, I, James J. Napoli, declare that (1) I am a Patent Attorney authorized to practice before the Patent and Trademark Office and have general authority from Lilly ICOS LLC to act on its behalf in patent matters; that (2) I have reviewed and understand the contents of this application for extension of U.S. Patent No. 5,859,006; that (3) I believe the patent is subject to extension pursuant to 37 C.F.R. §1.710; that (4) I believe the length of extension claimed is fully justified under 35 U.S.C. §156 and applicable regulations; and that (5) I believe the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

I further declare that all statements made herein of 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 extension issuing thereon.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

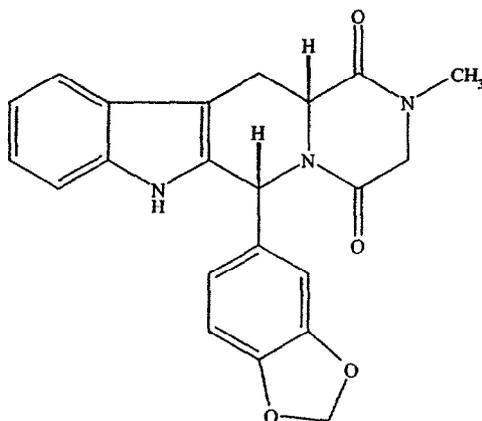
By 
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Chicago, Illinois
January 9, 2004

CIALIS[®] (tadalafil) tablets

DESCRIPTION

CIALIS[®] (tadalafil), an oral treatment for erectile dysfunction, is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula C₂₂H₁₉N₃O₄ representing a molecular weight of 389.41. The structural formula is:



The chemical designation is pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

CIALIS is available as film-coated, almond-shaped tablets for oral administration. Each tablet contains 5, 10, or 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY

Mechanism of Action

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation.

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas.

In vitro studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5

than for PDE3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10 and 14-fold more potent for PDE5 than for PDE11A1, an enzyme found in human skeletal muscle. Tadalafil inhibits human recombinant PDE11A1 activity at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

Pharmacokinetics

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once-daily dosing, and exposure is approximately 1.6-fold greater than after a single dose. Tadalafil is eliminated predominantly by hepatic metabolism, mainly by cytochrome P450 3A4 (CYP3A4). The concomitant use of potent CYP3A4 inhibitors such as ritonavir or ketoconazole resulted in significant increases in tadalafil AUC values (*see PRECAUTIONS and DOSAGE AND ADMINISTRATION*). Mean tadalafil concentrations measured after the administration of a single oral dose of 20 mg to healthy male subjects are depicted in Figure 1.

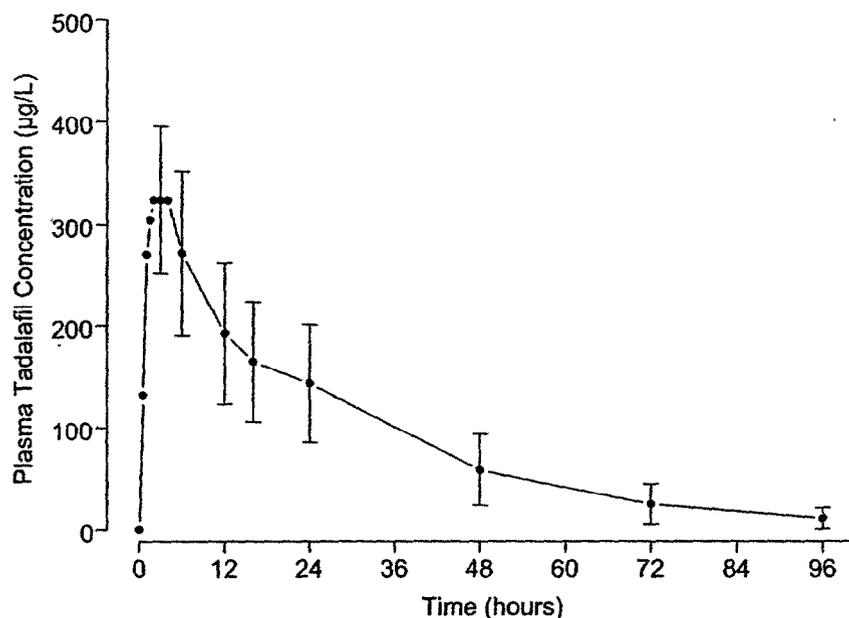


Figure 1: Plasma tadalafil concentrations (mean \pm SD) following a single 20-mg tadalafil dose

Absorption — After single oral-dose administration, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food; thus CIALIS may be taken with or without food.

Distribution — The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism — Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. *In vitro* data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination — The mean oral clearance for tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Pharmacokinetics in Special Populations

Geriatric — Healthy male elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered (*see Geriatric Use under PRECAUTIONS*).

Pediatric — Tadalafil has not been evaluated in individuals less than 18 years old.

Hepatic Impairment — In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C). Therefore, for patients with mild or moderate hepatic impairment, the maximum dose should not exceed 10 mg, and use in patients with severe hepatic impairment is not recommended (*see DOSAGE AND ADMINISTRATION*).

Renal Insufficiency — In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.1-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with moderate renal impairment. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain. The dose of tadalafil should be limited to 5 mg not more than once daily in patients with severe renal insufficiency or end-stage renal disease. A starting dose of 5 mg not more than once daily is recommended for patients with moderate renal insufficiency; the maximum recommended dose is 10 mg not more than once in every 48 hours. No dose adjustment is required in patients with mild renal insufficiency (*see DOSAGE AND ADMINISTRATION*).

Patients with Diabetes Mellitus — In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

Pharmacodynamics

Effects on Blood Pressure — Tadalafil 20 mg administered to healthy male subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively). In addition, there was no significant effect on heart rate.

Effects on Blood Pressure when CIALIS is Administered with Nitrates — In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of CIALIS in patients taking any form of nitrates is contraindicated (*see* CONTRAINDICATIONS).

A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre-specified timepoints, following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). The objective of the study was to determine when, after tadalafil dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood-pressure lowering at this timepoint. After 48 hours, the interaction was not detectable (*see* Figure 2).

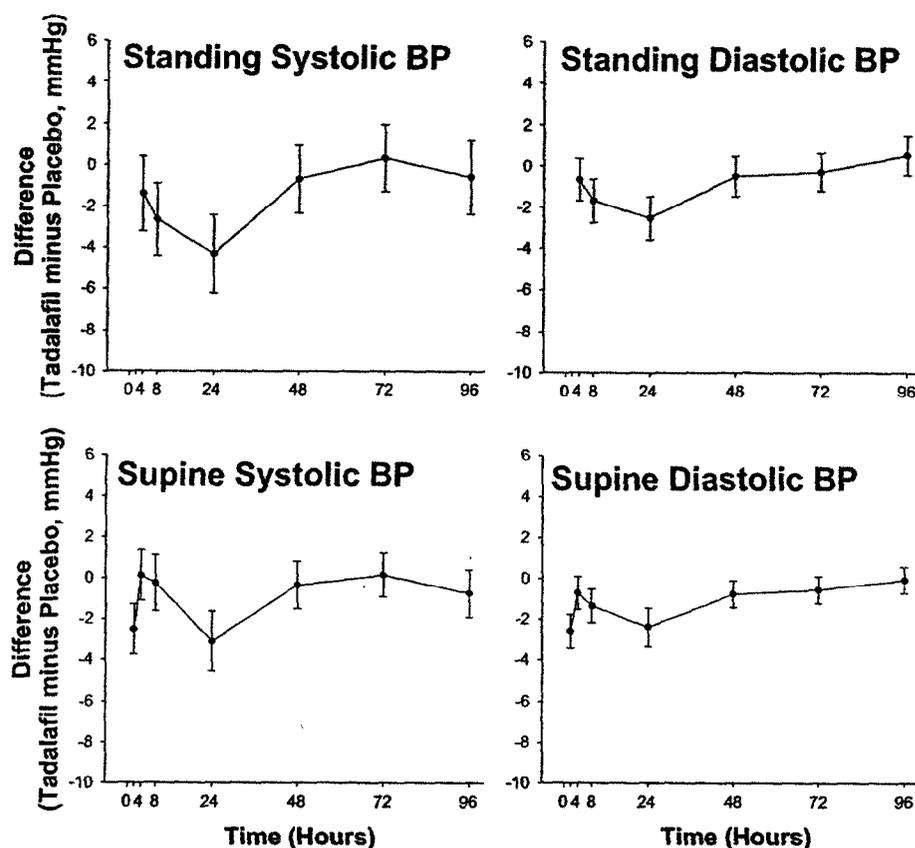


Figure 2: Mean Maximal Change in Blood Pressure (Tadalafil Minus Placebo, Point Estimate with 90% CI) in Response to Sublingual Nitroglycerin at 2 (Supine Only), 4, 8, 24, 48, 72, and 96 Hours after the Last Dose of Tadalafil 20 mg or Placebo

Therefore, CIALIS administration with nitrates is contraindicated. In a patient who has taken CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring (*see CONTRAINDICATIONS*).

Effects on Exercise Stress Testing — The effects of tadalafil on cardiac function, hemodynamics, and exercise tolerance were investigated in a single clinical pharmacology study. In this blinded crossover trial, 23 subjects with stable coronary artery disease and evidence of exercise-induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time was 3 seconds (tadalafil 10 mg minus placebo), which represented no clinically meaningful difference. Further statistical analysis demonstrated that tadalafil was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some subjects who received tadalafil followed by sublingual nitroglycerin in the post-exercise period, clinically significant reductions in blood pressure were observed, consistent with the augmentation by tadalafil of the blood-pressure-lowering effects of nitrates.

Effects on Vision — Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular

pressure, or pupillometry. Across all clinical studies with CIALIS, reports of changes in color vision were rare (<0.1% of patients).

Effects on Sperm Characteristics — There were no clinically relevant effects on sperm concentration, sperm count, motility, or morphology in humans in placebo-controlled studies of daily doses of tadalafil 10 mg (N=204) or 20 mg (N=217) for 6 months. In addition, tadalafil had no effect on serum levels of testosterone, luteinizing hormone, or follicle stimulating hormone.

Effects on Cardiac Electrophysiology — The effect of a single 100-mg dose of tadalafil on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blinded, placebo, and active (intravenous ibutilide)-controlled crossover study in 90 healthy males aged 18 to 53 years. The mean change in QT_c (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (two-sided 90% CI=1.9, 5.1). The mean change in QT_c (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (two-sided 90% CI=1.2, 4.4). A 100-mg dose of tadalafil (5 times the highest recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with potent CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100-mg dose of tadalafil compared to placebo was 3.1 beats per minute.

Clinical Studies

The efficacy and safety of tadalafil in the treatment of erectile dysfunction has been evaluated in 22 clinical trials of up to 24-weeks duration, involving over 4000 patients. CIALIS, when taken as needed up to once daily, was shown to be effective in improving erectile function in men with erectile dysfunction (ED).

Study Design — CIALIS was studied in the general ED population in 7 randomized, multicenter, double-blinded, placebo-controlled, parallel-arm design, primary efficacy and safety studies of 12-weeks duration. Two of these studies were conducted in the United States and 5 were conducted in centers outside the US. Additional efficacy and safety studies were performed in ED patients with diabetes mellitus and in patients who developed ED status post bilateral nerve-sparing radical prostatectomy.

In these 7 trials, CIALIS was taken as needed, at doses ranging from 2.5 to 20 mg, up to once daily. Patients were free to choose the time interval between dose administration and the time of sexual attempts. Food and alcohol intake were not restricted.

Several assessment tools were used to evaluate the effect of CIALIS on erectile function. The 3 primary outcome measures were the Erectile Function (EF) domain of the International Index of Erectile Function (IIEF) and Questions 2 and 3 from Sexual Encounter Profile (SEP). The IIEF is a 4-week recall questionnaire that was administered at the end of a treatment-free baseline period and subsequently at follow-up visits after randomization. The IIEF EF domain has a 30-point total score, where higher scores reflect better erectile function. SEP is a diary in which patients recorded each sexual attempt made throughout the study. SEP Question 2 asks, "Were you able to insert your penis into your partner's vagina?" SEP Question 3 asks, "Did your erection last long enough for you to have successful intercourse?" The overall percentage of successful attempts to insert the penis into the vagina (SEP2) and to maintain the erection for successful intercourse (SEP3) is derived for each patient.

Study Results —

ED Population in US Trials — The 2 primary US efficacy and safety trials included a total of 402 men with erectile dysfunction, with a mean age of 59 years (range 27 to 87 years). The population was 78% White, 14% Black, 7% Hispanic, and 1% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (>90%) patients reported ED of at least 1-year duration. Study A was conducted primarily in academic centers.

Study B was conducted primarily in community-based urology practices. In each of these 2 trials, CIALIS 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (*see* Table 1). The treatment effect of CIALIS did not diminish over time.

Table 1: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in the Two Primary US Trials

	Study A			Study B		
	Placebo (N=49)	CIALIS 20 mg (N=146)	p-value	Placebo (N=48)	CIALIS 20 mg (N=159)	p-value
EF Domain Score						
Endpoint	13.5	19.5		13.6	22.5	
Change from baseline	-0.2	6.9	<.001	0.3	9.3	<.001
Insertion of Penis (SEP2)						
Endpoint	39%	62%		43%	77%	
Change from baseline	2%	26%	<.001	2%	32%	<.001
Maintenance of Erection (SEP3)						
Endpoint	25%	50%		23%	64%	
Change from baseline	5%	34%	<.001	4%	44%	<.001

General ED Population in Trials Outside the US — The 5 primary efficacy and safety studies conducted in the general ED population outside the US included 1112 patients, with a mean age of 59 years (range 21 to 82 years). The population was 76% White, 1% Black, 3% Hispanic, and 20% of other ethnicities, and included patients with ED of various severities, etiologies (organic, psychogenic, mixed), and with multiple co-morbid conditions, including diabetes mellitus, hypertension, and other cardiovascular disease. Most (90%) patients reported ED of at least 1-year duration. In these 5 trials, CIALIS 5, 10, and 20 mg showed clinically meaningful and statistically significant improvements in all 3 primary efficacy variables (*see* Tables 2, 3, and 4). The treatment effect of CIALIS did not diminish over time.

Table 2: Mean Endpoint and Change from Baseline for the EF Domain of the IIEF in the General ED Population in Five Primary Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	15.0 [0.7]	17.9 [4.0]	20.0 [5.6]	
		<i>p</i> =.006	<i>p</i> <.001	
Study D				
Endpoint [Change from baseline]	14.4 [1.1]	17.5 [5.1]	20.6 [6.0]	
		<i>p</i> =.002	<i>p</i> <.001	
Study E				
Endpoint [Change from baseline]	18.1 [2.6]		22.6 [8.1]	25.0 [8.0]
			<i>p</i> <.001	<i>p</i> <.001
Study F*				
Endpoint [Change from baseline]	12.7 [-1.6]			22.8 [6.8]
				<i>p</i> <.001
Study G				
Endpoint [Change from baseline]	14.5 [-0.9]		21.2 [6.6]	23.3 [8.0]
			<i>p</i> <.001	<i>p</i> <.001

* Treatment duration in Study F was 6 months

Table 3: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 2 (“Were you able to insert your penis into the partner’s vagina?”) in the General ED Population in Five Pivotal Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	49% [6%]	57% [15%]	73% [29%]	
		<i>p</i> =.063	<i>p</i> <.001	
Study D				
Endpoint [Change from baseline]	46% [2%]	56% [18%]	68% [15%]	
		<i>p</i> =.008	<i>p</i> <.001	
Study E				
Endpoint [Change from baseline]	55% [10%]		77% [35%]	85% [35%]
			<i>p</i> <.001	<i>p</i> <.001
Study F*				
Endpoint [Change from baseline]	42% [-8%]			81% [27%]
				<i>p</i> <.001
Study G				
Endpoint [Change from baseline]	45% [-6%]		73% [21%]	76% [21%]
			<i>p</i> <.001	<i>p</i> <.001

* Treatment duration in Study F was 6 months

Table 4: Mean Post-Baseline Success Rate and Change from Baseline for SEP Question 3 (“Did your erection last long enough for you to have successful intercourse?”) in the General ED Population in Five Pivotal Trials Outside the US

	Placebo	CIALIS 5 mg	CIALIS 10 mg	CIALIS 20 mg
Study C				
Endpoint [Change from baseline]	26% [4%]	38% [19%]	58% [32%]	
		<i>p</i> =.040	<i>p</i> <.001	
Study D				
Endpoint [Change from baseline]	28% [4%]	42% [24%]	51% [26%]	
		<i>p</i> <.001	<i>p</i> <.001	
Study E				
Endpoint [Change from baseline]	43% [15%]		70% [48%]	78% [50%]
			<i>p</i> <.001	<i>p</i> <.001
Study F*				
Endpoint [Change from baseline]	27% [1%]			74% [40%]
				<i>p</i> <.001
Study G				
Endpoint [Change from baseline]	32% [5%]		57% [33%]	62% [29%]
			<i>p</i> <.001	<i>p</i> <.001

* Treatment duration in Study F was 6 months

In addition, there were improvements in EF domain scores, success rates based upon SEP Questions 2 and 3, and patient-reported improvement in erections across patients with ED of all degrees of disease severity while taking CIALIS, compared to patients on placebo.

Therefore, in all 7 primary efficacy and safety studies, CIALIS showed statistically significant improvement in patients’ ability to achieve an erection sufficient for vaginal penetration and to maintain the erection long enough for successful intercourse, as measured by the IIEF questionnaire and by SEP diaries.

Efficacy in ED Patients with Diabetes Mellitus — CIALIS was shown to be effective in treating ED in patients with diabetes mellitus. Patients with diabetes were included in all 7 primary efficacy studies in the general ED population (N=235) and in 1 study that specifically assessed CIALIS in ED patients with type 1 or type 2 diabetes (N=216). In this randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial, CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (see Table 5).

Table 5: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in ED Patients with Diabetes

	Placebo	CIALIS 10 mg	CIALIS 20 mg	
	(N=71)	(N=73)	(N=72)	p-value
EF Domain Score				
Endpoint [Change from baseline]	12.2 [0.1]	19.3 [6.4]	18.7 [7.3]	<.001
Insertion of Penis (SEP2)				
Endpoint [Change from baseline]	30% [-4%]	57% [22%]	54% [23%]	<.001
Maintenance of Erection (SEP3)				
Endpoint [Change from baseline]	20% [2%]	48% [28%]	42% [29%]	<.001

Efficacy in ED Patients following Radical Prostatectomy — CIALIS was shown to be effective in treating patients who developed ED following bilateral nerve-sparing radical prostatectomy. In 1 randomized, placebo-controlled, double-blinded, parallel-arm design prospective trial in this population (N=303), CIALIS demonstrated clinically meaningful and statistically significant improvement in erectile function, as measured by the EF domain of the IIEF questionnaire and Questions 2 and 3 of the SEP diary (see Table 6).

Table 6: Mean Endpoint and Change from Baseline for the Primary Efficacy Variables in a Study in Patients who Developed ED Following Bilateral Nerve-Sparing Radical Prostatectomy

	Placebo	CIALIS 20 mg	
	(N=102)	(N=201)	p-value
EF Domain Score			
Endpoint [Change from baseline]	13.3 [1.1]	17.7 [5.3]	<.001
Insertion of Penis (SEP2)			
Endpoint [Change from baseline]	32% [2%]	54% [22%]	<.001
Maintenance of Erection (SEP3)			
Endpoint [Change from baseline]	19% [4%]	41% [23%]	<.001

Studies to Determine the Optimal Use of CIALIS — Several studies were conducted with the objective of determining the optimal use of CIALIS in the treatment of ED. In 1 of these studies, the percentage of patients reporting successful erections within 30 minutes of dosing was determined. In this randomized, placebo-controlled, double-blinded trial, 223 patients were randomized to placebo, CIALIS 10, or 20 mg. Using a stopwatch, patients recorded the time following dosing at which a successful erection was obtained. A successful erection was defined as at least 1 erection in 4 attempts that led to successful intercourse. At or prior to 30 minutes, 35% (26/74), 38% (28/74), and 52% (39/75) of patients in the placebo, 10-, and 20-mg groups, respectively, reported successful erections as defined above.

Two studies were conducted to assess the efficacy of CIALIS at a given timepoint after dosing, specifically at 24 hours and at 36 hours after dosing.

In the first of these studies, 348 patients with ED were randomized to placebo or CIALIS 20 mg. Patients were encouraged to make 4 total attempts at intercourse; 2 attempts were to occur at 24 hours after dosing and 2 completely separate attempts were to occur at 36 hours after dosing. The results demonstrated a difference between the placebo group and the CIALIS group at each of the

pre-specified timepoints. At the 24-hour timepoint, (more specifically, 22 to 26 hours), 53/144 (37%) patients reported at least 1 successful intercourse in the placebo group versus 84/138 (61%) in the CIALIS 20-mg group. At the 36-hour timepoint (more specifically, 33 to 39 hours), 49/133 (37%) of patients reported at least 1 successful intercourse in the placebo group versus 88/137 (64%) in the CIALIS 20-mg group.

In the second of these studies, a total of 483 patients were evenly randomized to 1 of 6 groups: 3 different dosing groups (placebo, CIALIS 10, or 20 mg) that were instructed to attempt intercourse at 2 different times (24 and 36 hours post-dosing). Patients were encouraged to make 4 separate attempts at their assigned dose and assigned timepoint. In this study, the results demonstrated a statistically significant difference between the placebo group and the CIALIS groups at each of the pre-specified timepoints. At the 24-hour timepoint, the mean, per-patient percentage of attempts resulting in successful intercourse were 42, 56, and 67% for the placebo, CIALIS 10-, and 20-mg groups, respectively. At the 36-hour timepoint, the mean, per-patient percentage of attempts resulting in successful intercourse were 33, 56, and 62% for placebo, CIALIS 10-, and 20-mg groups, respectively.

INDICATIONS AND USAGE

CIALIS is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS

Nitrates — Administration of CIALIS to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, tadalafil was shown to potentiate the hypotensive effect of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway (*see Pharmacodynamics, Effects on Blood Pressure when CIALIS is Administered with Nitrates under CLINICAL PHARMACOLOGY*).

Alpha Blockers — Administration of CIALIS to patients taking any alpha-adrenergic antagonist other than 0.4 mg once-daily tamsulosin is contraindicated. In a drug-drug interaction study, when tadalafil 20 mg was administered to healthy subjects taking doxazosin (8 mg daily), there was a significant augmentation of the blood-pressure-lowering effect of doxazosin (*see Drug Interactions under PRECAUTIONS*).

Hypersensitivity — CIALIS is contraindicated for patients with a known hypersensitivity to tadalafil or any component of the tablet.

WARNINGS

Cardiovascular

General — Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatments for erectile dysfunction, including CIALIS, should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status.

Left Ventricular Outflow Obstruction — Patients with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators, including PDE5 inhibitors.

Patients Not Studied in Clinical Trials

The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for CIALIS, and, therefore, the use of CIALIS is not recommended in these groups until further information is available:

- patients with a myocardial infarction within the last 90 days

- patients with unstable angina or angina occurring during sexual intercourse
- patients with New York Heart Association Class 2 or greater heart failure in the last 6 months
- patients with uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension (>170/100 mm Hg)
- patients with a stroke within the last 6 months

In addition, patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

Prolonged Erection

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

PRECAUTIONS

Evaluation of erectile dysfunction should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options.

Before prescribing CIALIS, it is important to note the following:

Renal Insufficiency

CIALIS should be limited to 5 mg not more than once daily in patients with severe renal insufficiency or end-stage renal disease. The starting dose of CIALIS in patients with a moderate degree of renal insufficiency should be 5 mg not more than once daily, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. No dose adjustment is required in patients with mild renal insufficiency (*see Pharmacokinetics in Special Populations under CLINICAL PHARMACOLOGY*).

Hepatic Impairment

In patients with mild or moderate hepatic impairment, the dose of CIALIS should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of CIALIS in this group is not recommended (*see Pharmacokinetics in Special Populations under CLINICAL PHARMACOLOGY*).

Concomitant Use of Potent Inhibitors of Cytochrome P450 3A4 (CYP3A4)

CIALIS is metabolized predominantly by CYP3A4 in the liver. The dose of CIALIS should be limited to 10 mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, and itraconazole (*see Effects of Other Drugs on CIALIS under Drug Interactions*).

General

As with other PDE5 inhibitors, tadalafil has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, tadalafil 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mm Hg in healthy subjects (*see Clinical Studies under CLINICAL PHARMACOLOGY*). While this effect should not be of consequence in most patients, prior to prescribing CIALIS, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with significant left ventricular outflow obstruction or severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators.

The safety and efficacy of combinations of CIALIS and other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

CIALIS should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. CIALIS has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although CIALIS has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

Information for Patients

Physicians should discuss with patients the contraindication of CIALIS with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of CIALIS with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of CIALIS. In such a patient, who has taken CIALIS, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking CIALIS should seek immediate medical attention.

Physicians should inform their patients that concomitant use of CIALIS with alpha-adrenergic antagonists (other than 0.4 mg once-daily tamsulosin) is contraindicated because coadministration can lead to significant reductions in blood pressure.

Physicians should discuss with patients the potential for CIALIS to augment the blood-pressure-lowering effect of other anti-hypertensive medications.

Patients should be made aware that both alcohol and CIALIS, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Physicians should consider the potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and seek immediate medical attention.

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

The use of CIALIS offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

Patients should read the patient leaflet entitled "INFORMATION FOR THE PATIENT" before starting therapy with CIALIS and each time the prescription is renewed or refilled.

Drug Interactions

Effects of Other Drugs on CIALIS

Cytochrome P450 Inhibitors

CIALIS is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure (*see PRECAUTIONS and DOSAGE AND ADMINISTRATION*).

Ketoconazole — Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20-mg single-dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10-mg single-dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for tadalafil 10 mg alone.

HIV Protease inhibitor — Ritonavir (200 mg twice daily), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure (AUC) by 124% with no change in C_{max} , relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase tadalafil exposure (*see DOSAGE AND ADMINISTRATION*).

Based upon these results, in patients taking concomitant potent CYP3A4 inhibitors, the dose of CIALIS should not exceed 10 mg, and CIALIS should not be taken more frequently than once in every 72 hours (*see DOSAGE AND ADMINISTRATION*).

Other cytochrome P450 inhibitors — Although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure.

Cytochrome P450 Inducers

Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure.

Rifampin — Rifampin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10-mg single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted.

Gastrointestinal Drugs

H₂ antagonists — An increase in gastric pH resulting from administration of nizatidine had no significant effect on tadalafil pharmacokinetics.

Antacids — Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

Effects of CIALIS on Other Drugs

Drugs Metabolized by Cytochrome P450

CIALIS is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

CYP1A2 substrate — Tadalafil had no clinically significant effect on the pharmacokinetics of theophylline. When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP3A4 substrates — Tadalafil had no clinically significant effect on exposure (AUC) to midazolam or lovastatin.

CYP2C9 substrate — Tadalafil had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin.

Alcohol

Alcohol and PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. The interaction of tadalafil with alcohol was evaluated in 3 clinical pharmacology studies. In 2 of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately 6 ounces of 80-proof vodka in an 80-kg male, and tadalafil was administered at a dose of 10 mg in 1 study and 20 mg in another. In both these studies, all patients imbibed the entire alcohol dose within 10 minutes of starting. In one of these two studies, blood alcohol levels of 0.08% were confirmed. In these two studies, more patients had clinically significant decreases in blood pressure on the combination of tadalafil and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When tadalafil 20 mg was administered with a lower dose of alcohol (0.6 g/kg, which is equivalent to approximately 4 ounces of 80-proof vodka, administered in less than 10 minutes), orthostatic hypotension was not observed, dizziness occurred with similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated.

Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Both alcohol and CIALIS, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Anti-Hypertensives

PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected anti-hypertensive medications.

Alpha Blockers

Doxazosin — When tadalafil 20 mg was administered to healthy subjects taking doxazosin (8 mg daily), an alpha[1]-adrenergic blocker, there was significant augmentation of the blood-pressure-lowering effect of doxazosin.

Tamsulosin — In a clinical pharmacology study, when a single dose of tadalafil 20 mg was administered to healthy subjects taking 0.4 mg once-daily tamsulosin, a selective alpha[1A]-adrenergic blocker, no significant decreases in blood pressure were observed.

Therefore, based upon significant augmentation of the blood-pressure-lowering effect of doxazosin, an alpha[1]-adrenergic blocker, and no significant effect seen with 0.4 mg once-daily tamsulosin, a selective alpha[1A]-adrenergic blocker, administration of CIALIS to patients taking any alpha-adrenergic blocker other than 0.4 mg once-daily tamsulosin is contraindicated.

Other Anti-Hypertensive Agents

Amlodipine — A study was conducted to assess the interaction of amlodipine (5 mg daily) and tadalafil 10 mg. There was no effect of tadalafil on amlodipine blood levels and no effect of amlodipine on tadalafil blood levels. The mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking amlodipine was 3/2 mm Hg, compared to placebo. In a similar study using tadalafil 20 mg, there were no clinically significant differences between tadalafil and placebo in subjects taking amlodipine.

Metoprolol — A study was conducted to assess the interaction of sustained-release metoprolol (25 to 200 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking metoprolol was 5/3 mm Hg, compared to placebo.

Bendrofluazide — A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking bendrofluazide was 6/4 mm Hg, compared to placebo.

Enalapril — A study was conducted to assess the interaction of enalapril (10 to 20 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking enalapril was 4/1 mm Hg, compared to placebo.

Angiotensin II receptor blocker (and other anti-hypertensives) — A study was conducted to assess the interaction of angiotensin II receptor blockers and tadalafil 20 mg. Subjects in the study were taking any marketed angiotensin II receptor blocker, either alone, as a component of a combination product, or as part of a multiple anti-hypertensive regimen. Following dosing, ambulatory measurements of blood pressure revealed differences between tadalafil and placebo of 8/4 mm Hg in systolic/diastolic blood pressure.

Aspirin

Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Tadalafil was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 400 mg/kg/day. Systemic drug exposures, as measured by AUC of unbound tadalafil, were approximately 10-fold for mice, and 14- and 26-fold for male and female rats, respectively, the exposures in human males given Maximum Recommended Human Dose (MRHD) of 20 mg.

Tadalafil was not mutagenic in the *in vitro* bacterial Ames assays or the forward mutation test in mouse lymphoma cells. Tadalafil was not clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes or the *in vivo* rat micronucleus assays.

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day, a dose producing AUCs for unbound tadalafil of 14-fold for males or 26-fold for females the exposures observed in human males given the MRHD of 20 mg. In beagle dogs given tadalafil daily for 3 to 12 months, there was treatment-related non-reversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20-100% of the dogs that resulted in a decrease in spermatogenesis in 40-75% of the dogs at doses of ≥ 10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect-level (NOAEL) (10 mg/kg/day) for unbound tadalafil was similar to that expected in humans at the MRHD of 20 mg.

There were no treatment-related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

In men, there were no clinically relevant effects on sperm concentration, sperm count, motility, or morphology in placebo-controlled studies of daily doses of tadalafil 10 mg (N=204) or 20 mg (N=217) for 6 months. In addition, tadalafil had no effect on serum levels of testosterone, luteinizing hormone, or follicle stimulating hormone in males.

Animal Toxicology

Animal studies showed vascular inflammation in tadalafil-treated mice, rats, and dogs. In mice and rats, lymphoid necrosis and hemorrhage were seen in the spleen, thymus, and mesenteric lymph nodes at unbound tadalafil exposure of 2- to 33-fold above the human exposure (AUCs) at the MRHD of 20 mg. In dogs, an increased incidence of disseminated arteritis was observed in 1- and 6-month studies at unbound tadalafil exposure of 1- to 54-fold above the human exposure (AUC) at the MRHD of 20 mg. In a 12-month dog study, no disseminated arteritis was observed, but 2 dogs exhibited marked decreases in white blood cells (neutrophils) and moderate decreases in platelets with inflammatory signs at unbound tadalafil exposures of approximately 14- to 18-fold the human exposure at the MRHD of 20 mg. The abnormal blood-cell findings were reversible within 2 weeks upon removal of the drug.

Pregnancy, Nursing Mothers, and Pediatric Use

CIALIS is not indicated for use in newborns, children, or women.

Tadalafil and/or its metabolites cross the placenta, resulting in fetal exposure in rats. Tadalafil and/or its metabolites were secreted into the milk in lactating rats at concentrations approximately 2.4-fold greater than found in the plasma. Following a single-oral dose of 10 mg/kg, approximately 0.1% of the total radioactive dose was excreted into the milk within 3 hours. It is not known if tadalafil and/or its metabolites is excreted in human breast milk. Use of tadalafil in nursing mothers is not recommended.

Pregnancy Category B — There was no evidence of teratogenicity, embryotoxicity, or fetotoxicity in rat or mouse fetuses that received up to 1000 mg/kg/day during the major organ development. Plasma exposure at this dose is approximately 11-fold greater than the AUC values for unbound tadalafil in humans given the MRHD of 20 mg. In a rat prenatal and postnatal development study at doses of 60, 200, and 1000 mg/kg, there was a reduction in postnatal survival of pups. The no-observed-effect-level (NOEL) for maternal toxicity was 200 mg/kg/day and for developmental toxicity was 30 mg/kg/day, which gives approximately 16- and 10-fold exposure multiples, respectively, of the human AUC for the MRHD dose of 20 mg. There are no adequate and well-controlled studies of tadalafil in pregnant women.

Geriatric Use

Approximately 25% of patients in the primary efficacy and safety studies of tadalafil were greater than 65 years of age. No overall differences in efficacy and safety were observed between older and younger patients. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered (*see Special Populations under CLINICAL PHARMACOLOGY*).

ADVERSE REACTIONS

Tadalafil was administered to over 5700 men (mean age 59, range 19 to 87 years) during clinical trials worldwide. Over 1000 patients were treated for 1 year or longer and over 1300 patients were treated for 6 months or more.

In placebo-controlled Phase 3 clinical trials, the discontinuation rate due to adverse events in patients treated with tadalafil 10 or 20 mg was 3.1%, compared to 1.4% in placebo-treated patients.

When tadalafil was taken as recommended in the placebo-controlled clinical trials, the following adverse events were reported (*see Table 7*):

Table 7: Treatment-Emergent Adverse Events Reported by $\geq 2\%$ of Patients Treated with Tadalafil (10 or 20 mg) and More Frequent on Drug than Placebo in the Eight Primary Placebo-Controlled Phase 3 Studies (Including a Study in Patients with Diabetes)

Adverse Event	Placebo (N=476)	Tadalafil 5 mg (N=151)	Tadalafil 10 mg (N=394)	Tadalafil 20 mg (N=635)
Headache	5%	11%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal congestion	1%	2%	3%	3%
Flushing*	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

* The term flushing includes: facial flushing and flushing

Back pain or myalgia was reported at incidence rates described in Table 7. In tadalafil clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbancy. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported infrequently (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required treatment, a mild narcotic (e.g. codeine) was used. Overall, approximately 0.5% of all tadalafil-treated subjects discontinued treatment as a consequence of back pain/myalgia. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology.

Across all studies with any tadalafil dose, reports of changes in color vision were rare (<0.1% of patients).

The following section identifies additional, less frequent events (<2%) reported in controlled clinical trials; a causal relationship of these events to CIALIS is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and reports too imprecise to be meaningful:

Body as a whole: asthenia, face edema, fatigue, pain

Cardiovascular: angina pectoris, chest pain, hypotension, hypertension, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia

Digestive: abnormal liver function tests, diarrhea, dry mouth, dysphagia, esophagitis, gastroesophageal reflux, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting

Musculoskeletal: arthralgia, neck pain

Nervous: dizziness, hypesthesia, insomnia, paresthesia, somnolence, vertigo

Respiratory: dyspnea, epistaxis, pharyngitis

Skin and Appendages: pruritus, rash, sweating

Ophthalmologic: blurred vision, changes in color vision, conjunctivitis (including conjunctival hyperemia), eye pain, lacrimation increase, swelling of eyelids

Urogenital: erection increased, spontaneous penile erection

OVERDOSAGE

Single doses up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Hemodialysis contributes negligibly to tadalafil elimination.

DOSAGE AND ADMINISTRATION

The recommended starting dose of CIALIS in most patients is 10 mg, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.

CIALIS was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of CIALIS, this should be taken into consideration.

CIALIS may be taken without regard to food.

Renal Insufficiency — No dose adjustment is required in patients with mild renal insufficiency. For patients with moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency, a starting dose of

5 mg not more than once daily is recommended, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. For patients with severe (creatinine clearance <30 mL/min) renal insufficiency on hemodialysis, the maximum recommended dose is 5 mg (*see General and Patients with Renal Insufficiency under PRECAUTIONS and Pharmacokinetics in Special Populations under CLINICAL PHARMACOLOGY*).

Hepatic Impairment — For patients with mild or moderate degrees of hepatic impairment (Child-Pugh Class A or B), the dose of CIALIS should not exceed 10 mg once daily. In patients with severe hepatic impairment (Child-Pugh Class C), the use of CIALIS is not recommended (*see Patients with Hepatic Impairment under PRECAUTIONS and Pharmacokinetics in Special Populations under CLINICAL PHARMACOLOGY*).

Concomitant Medications — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of CIALIS is 10 mg, not to exceed once every 72 hours (*see General and Drug Interactions under PRECAUTIONS*).

Concomitant use of nitrates in any form and alpha-adrenergic blockers (other than 0.4 mg once-daily tamsulosin) is contraindicated (*see CONTRAINDICATIONS and Drug Interactions under PRECAUTIONS*).

Geriatrics — No dose adjustment is required in patients >65 years of age.

HOW SUPPLIED

CIALIS® (tadalafil) is supplied as follows:

Three strengths of film-coated, almond-shaped tablets are available in different sizes and different shades of yellow, and supplied in the following package sizes:

5-mg tablets debossed with "C 5"

Bottles of 30 NDC 0002-4462-30

10-mg tablets debossed with "C 10"

Bottles of 30 NDC 0002-4463-30

20-mg tablets debossed with "C 20"

Bottles of 30 NDC 0002-4464-30

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Keep out of reach of children.

Literature issued November, 2003

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NL 3534 AMP

PRINTED IN USA

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Patient Information

CIALIS[®] (See-AL-iss)
(tadalafil)
tablets

Read the Patient Information about CIALIS before you start taking it and again each time you get a refill. There may be new information. You may also find it helpful to share this information with your partner. This leaflet does not take the place of talking with your doctor. You and your doctor should talk about CIALIS when you start taking it and at regular checkups. If you do not understand the information, or have questions, talk with your doctor or pharmacist.

What important information should you know about CIALIS?

CIALIS can cause your blood pressure to drop suddenly to an unsafe level if it is taken with certain other medicines. You could get dizzy, faint, or have a heart attack or stroke.

Do not take CIALIS if you:

- take any medicines called “nitrates.”
- use recreational drugs called “poppers” like amyl nitrate and butyl nitrate.
- take medicines called alpha blockers, other than Flomax[®] (tamsulosin HCl) 0.4 mg daily.

(See “Who should not take CIALIS?”)

Tell all your healthcare providers that you take CIALIS. If you need emergency medical care for a heart problem, it will be important for your healthcare provider to know when you last took CIALIS.

After taking a single tablet, some of the active ingredient of CIALIS remains in your body for more than 2 days. The active ingredient can remain longer if you have problems with your kidneys or liver, or you are taking certain other medications (see “Can other medications affect CIALIS?”).

What is CIALIS?

CIALIS is a prescription medicine taken by mouth for the treatment of erectile dysfunction (ED) in men.

ED is a condition where the penis does not harden and expand when a man is sexually excited, or when he cannot keep an erection. A man who has trouble getting or keeping an erection should see his doctor for help if the condition bothers him. CIALIS may help a man with ED get and keep an erection when he is sexually excited.

CIALIS does not:

- cure ED
- increase a man’s sexual desire
- protect a man or his partner from sexually transmitted diseases, including HIV. Speak to your doctor about ways to guard against sexually transmitted diseases.
- serve as a male form of birth control

CIALIS is only for men with ED. CIALIS is not for women or children. CIALIS must be used only under a doctor's care.

How does CIALIS work?

When a man is sexually stimulated, his body's normal physical response is to increase blood flow to his penis. This results in an erection. CIALIS helps increase blood flow to the penis and may help men with ED get and keep an erection satisfactory for sexual activity. Once a man has completed sexual activity, blood flow to his penis decreases, and his erection goes away.

Who can take CIALIS?

Talk to your doctor to decide if CIALIS is right for you.

CIALIS has been shown to be effective in men over the age of 18 years who have erectile dysfunction, including men with diabetes or who have undergone prostatectomy.

Who should not take CIALIS?

Do not take CIALIS if you:

- **take any medicines called "nitrates"** (See "What important information should you know about CIALIS?"). Nitrates are commonly used to treat angina. Angina is a symptom of heart disease and can cause pain in your chest, jaw, or down your arm.

Medicines called nitrates include nitroglycerin that is found in tablets, sprays, ointments, pastes, or patches. Nitrates can also be found in other medicines such as isosorbide dinitrate or isosorbide mononitrate. Some recreational drugs called "poppers" also contain nitrates, such as amyl nitrate and butyl nitrate. Do not use CIALIS if you are using these drugs. Ask your doctor or pharmacist if you are not sure if any of your medicines are nitrates.

- **take medicines called "alpha blockers", other than Flomax[®] 0.4 mg daily.** Alpha blockers are sometimes prescribed for prostate problems or high blood pressure. If CIALIS is taken with alpha blockers other than Flomax[®] 0.4 mg daily, your blood pressure could suddenly drop to an unsafe level. You could get dizzy and faint.
- **you have been told by your healthcare provider to not have sexual activity because of health problems.** Sexual activity can put an extra strain on your heart, especially if your heart is already weak from a heart attack or heart disease.
- **are allergic to CIALIS or any of its ingredients.** The active ingredient in CIALIS is called tadalafil. See the end of this leaflet for a complete list of ingredients.

What should you discuss with your doctor before taking CIALIS?

Before taking CIALIS, tell your doctor about all your medical problems, including if you:

- **have heart problems** such as angina, heart failure, irregular heartbeats, or have had a heart attack. Ask your doctor if it is safe for you to have sexual activity.
- **have low blood pressure or have high blood pressure that is not controlled**
- **have had a stroke**
- **have liver problems**
- **have kidney problems or require dialysis**
- **have retinitis pigmentosa, a rare genetic (runs in families) eye disease**
- **have stomach ulcers**

- **have a bleeding problem**
- **have a deformed penis shape** or Peyronie's disease
- **have had an erection that lasted more than 4 hours**
- **have blood cell problems** such as sickle cell anemia, multiple myeloma, or leukemia

Can other medications affect CIALIS?

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. CIALIS and other medicines may affect each other. Always check with your doctor before starting or stopping any medicines. Especially tell your doctor if you take any of the following:

- medicines called nitrates (See "What important information should you know about CIALIS?")
- medicines called alpha blockers. These include Hytrin[®] (terazosin), Flomax[®] (tamsulosin), Cardura[®] (doxazosin), Minipress[®] (prazosin) or Uroxatral[®] (alfuzosin).
- ritonavir (Norvir[®]) or indinavir (Crixivan[®])
- ketoconazole or itraconazole (such as Nizoral[®] or Sporanox[®])
- erythromycin
- other medicines or treatments for ED

How should you take CIALIS?

Take CIALIS exactly as your doctor prescribes. CIALIS comes in different doses (5 mg, 10 mg, and 20 mg). For most men, the recommended starting dose is 10 mg. **CIALIS should be taken no more than once a day.** Some men can only take a low dose of CIALIS because of medical conditions or medicines they take. Your doctor will prescribe the dose that is right for you.

- If you have kidney problems, your doctor may start you on a lower dose of CIALIS.
- If you have kidney or liver problems or you are taking certain medications, your doctor may limit your highest dose of CIALIS to 10 mg and may also limit you to one tablet in 48 hours (2 days) or one tablet in 72 hours (3 days).

Take one CIALIS tablet before sexual activity. In some patients, the ability to have sexual activity was improved at 30 minutes after taking CIALIS when compared to a sugar pill. The ability to have sexual activity was improved up to 36 hours after taking CIALIS when compared to a sugar pill. You and your doctor should consider this in deciding when you should take CIALIS prior to sexual activity. Some form of sexual stimulation is needed for an erection to happen with CIALIS. CIALIS may be taken with or without meals.

Do not change your dose of CIALIS without talking to your doctor. Your doctor may lower your dose or raise your dose, depending on how your body reacts to CIALIS.

Do not drink alcohol to excess when taking CIALIS (for example, 5 glasses of wine or 5 shots of whiskey). When taken in excess, alcohol can increase your chances of getting a headache or getting dizzy, increasing your heart rate, or lowering your blood pressure.

If you take too much CIALIS, call your doctor or emergency room right away.

What are the possible side effects of CIALIS?

The most common side effects with CIALIS are headache, indigestion, back pain, muscle aches, flushing, and stuffy or runny nose. These side effects usually go away after a few hours. Patients who

get back pain and muscle aches usually get it 12 to 24 hours after taking CIALIS. Back pain and muscle aches usually go away by themselves within 48 hours. Call your doctor if you get a side effect that bothers you or one that will not go away.

CIALIS may uncommonly cause:

- **an erection that won't go away (priapism).** If you get an erection that lasts more than 4 hours, get medical help right away. Priapism must be treated as soon as possible or lasting damage can happen to your penis including the inability to have erections.
- vision changes, such as seeing a blue tinge to objects or having difficulty telling the difference between the colors blue and green.

These are not all the side effects of CIALIS. For more information, ask your doctor or pharmacist.

How should CIALIS be stored?

- Store CIALIS at room temperature between 59° and 86°F (15° and 30°C).
- **Keep CIALIS and all medicines out of the reach of children.**

General Information about CIALIS:

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use CIALIS for a condition for which it was not prescribed. Do not give CIALIS to other people, even if they have the same symptoms that you have. It may harm them.

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

For more information you can also visit www.cialis.com, or call 1-877-242-5441.

What are the ingredients of CIALIS?

Active Ingredient: tadalafil

Inactive Ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

Rx only

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US005859006A

United States Patent [19][11] **Patent Number:** 5,859,006**Daugan**[45] **Date of Patent:** Jan. 12, 1999[54] **TETRACYCLIC DERIVATIVES; PROCESS OF PREPARATION AND USE**[75] **Inventor:** Alain Claude-Marie Daugan, Les Ulis, France[73] **Assignee:** ICOS Corporation, Bothell, Wash.[21] **Appl. No.:** 669,389[22] **PCT Filed:** Jan. 19, 1995[86] **PCT No.:** PCT/EP95/00183

§ 371 Date: Jul. 17, 1996

§ 102(e) Date: Jul. 17, 1996

[87] **PCT Pub. No.:** WO95/19978

PCT Pub. Date: Jul. 27, 1995

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Jan. 21, 1994 [GB] United Kingdom 9401090

[51] **Int. Cl.^o** A01N 43/58; A01N 43/42; C07D 241/36; C07D 471/00[52] **U.S. Cl.** 514/249; 514/250; 514/292; 544/343; 546/81; 546/85[58] **Field of Search** 544/343; 514/249, 514/250, 292; 546/81, 85[56] **References Cited****U.S. PATENT DOCUMENTS**

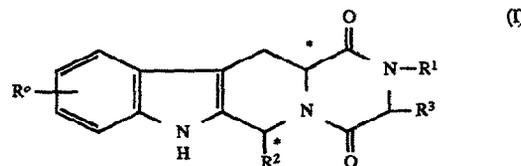
3,644,384	2/1972	Schulenberg	260/295
3,717,638	2/1973	Schulenberg	260/268
3,917,599	11/1975	Saxena et al.	260/268

FOREIGN PATENT DOCUMENTS

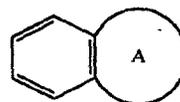
0 357 122A	3/1990	European Pat. Off.
0 362 555A	4/1990	European Pat. Off.
1454171	10/1976	United Kingdom

OTHER PUBLICATIONSDellouve-Courillon et al., *Tetrahedron*, 46(9), 3245-66 (1990).Brana et al., *Synth Comm.*, 20(12), 1793-1810 (1990).Saxena et al., *Journal of Medicinal Chemistry*, 16(5), 1973, 560-564.Ishida et al., *Chem. Pharm. Bull.*, 33(8), 1985, 3237-3249.*Primary Examiner*—Mukund J. Shah*Assistant Examiner*—Tamthom T. Ngo*Attorney, Agent, or Firm*—Marshall, O'Toole, Gerstein, Murray & Borun[57] **ABSTRACT**

A compound of formula (I)



and salts and solvates thereof, in which:

R⁰ represents hydrogen, halogen or C₁₋₆alkyl;R¹ represents hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, haloC₁₋₆alkyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkylC₁₋₃alkyl, arylC₁₋₃alkyl or heteroarylC₁₋₃alkyl; R² represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring

attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R³ represents hydrogen or C₁₋₃alkyl, or R¹ and R³ together represent a 3- or 4-membered alkyl or alkenyl chain.

A compound of formula (I) is a potent and selective inhibitor of cyclic guanosine 3', 5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders.

15 Claims, No Drawings

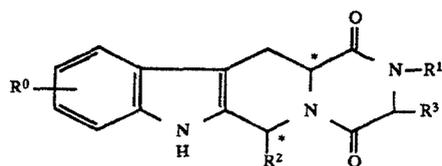
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TETRACYCLIC DERIVATIVES; PROCESS OF PREPARATION AND USE

This is a 371 application of Pct/EP filed on Jan. 19, 1995.

This invention relates to a series of tetracyclic derivatives, to processes for their preparation, pharmaceutical compositions containing them, and their use as therapeutic agents. In particular, the invention relates to tetracyclic derivatives which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having utility in a variety of therapeutic areas where such inhibition is thought to be beneficial, including the treatment of cardiovascular disorders.

Thus, according to a first aspect, the present invention provides compounds of formula (I)

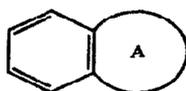


and salts and solvates (e.g. hydrates) thereof, in which:

R⁰ represents hydrogen, halogen or C₁₋₆alkyl;

R¹ represents hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, haloC₁₋₆alkyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkylC₁₋₃alkyl, arylC₁₋₃alkyl or heteroarylC₁₋₃alkyl;

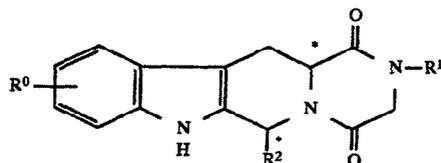
R² represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring



attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R³ represents hydrogen or C₁₋₃alkyl, or R¹ and R³ together represent a 3- or 4- membered alkyl or alkenyl chain.

There is further provided by the present invention a subgroup of compounds of formula (I), the subgroup comprising compounds of formula (Ia)



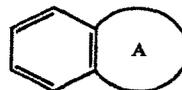
and salts and solvates (e.g. hydrates) thereof, in which:

R⁰ represents hydrogen, halogen or C₁₋₆alkyl;

R¹ represents hydrogen, C₁₋₆alkyl, haloC₁₋₆alkyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkylC₁₋₃alkyl, arylC₁₋₃alkyl or heteroarylC₁₋₃alkyl; and

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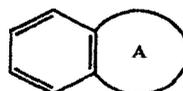
R² represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring



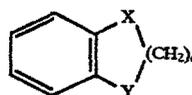
attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen.

Within R¹ above, the term "aryl" as part of an arylC₁₋₃alkyl group means phenyl or phenyl substituted by one or more (e.g. 1, 2 or 3) substituents, selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy and methylenedioxy. The term "heteroaryl" as part of a heteroarylC₁₋₃alkyl group means thienyl, furyl or pyridyl each optionally substituted by one or more (e.g. 1, 2 or 3) substituents selected from halogen, C₁₋₆alkyl and C₁₋₆alkoxy. The term "C₃₋₈cycloalkyl" as a group or part of a C₃₋₈cycloalkylC₁₋₃alkyl group means a monocyclic ring comprising three to eight carbon atoms. Examples of suitable cycloalkyl rings include the C₃₋₆cycloalkyl rings cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Within R² above, optional benzene ring substituents are selected from one or more (e.g. 1, 2 or 3) atoms or groups comprising halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, —CO₂R^b, haloC₁₋₆alkyl, haloC₁₋₆alkoxy, cyano, nitro and NR^aR^b, where R^a and R^b are each hydrogen or C₁₋₆alkyl, or R^a may also represent C₂₋₇alkanoyl or C₁₋₆alkylsulphonyl. Optional substituents for the remaining ring systems are selected from one or more (e.g. 1, 2 or 3) atoms or groups comprising halogen, C₁₋₆alkyl, C₁₋₆alkoxy and arylC₁₋₃alkyl as defined above. The bicyclic ring



may, for example, represent naphthalene, a heterocycle such as benzoxazole, benzothiazole, benzisoxazole, benzimidazole, quinoline, indole, benzothiophene or benzofuran or



(Ia) (where n is an integer 1 or 2 and X and Y may each represent CH₂, O, S or NH).

In the above definitions, the term "alkyl" as a group or part of a group means a straight chain or, where available, a branched chain alkyl moiety. For example, it may represent a C₁₋₄alkyl function as represented by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. The term "alkenyl" as used herein includes straight-chained and branched alkenyl groups, such as vinyl and allyl, groups. The term "alkynyl" as used herein includes straight-chained and branched alkynyl groups, suitably acetylene. The term "halogen" herein means a fluorine, chlorine, bromine or iodine atom. The term "haloC₁₋₆alkyl" means an alkyl group

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as defined above comprising one to six carbon atoms substituted at one or more carbon atoms by one or more (e.g. 1, 2 or 3) halogen atoms. Similarly, a haloC₁₋₆alkoxy group is a haloC₁₋₆alkyl group as defined above linked to the R² benzene ring via an oxygen atom. Examples of haloC₁₋₆alkyl groups include trifluoromethyl and 2,2,2-trifluoroethyl. An example of a haloC₁₋₆alkoxy group is trifluoromethoxy. The term "C₂₋₇alkanoyl" means a C₁₋₆alkylcarbonyl group where the C₁₋₆alkyl portion is as defined above. An example of a suitable C₂₋₇alkanoyl group is the C₂alkanoyl group acetyl.

It will be appreciated that when R⁰ is a halogen atom or a C₁₋₆alkyl group this substituent may be sited at any available position on the phenyl portion of the tetracyclic ring. However, a particular site of attachment is the ring 10-position.

The compounds of formula (I) may contain two or more asymmetric centres and thus can exist as enantiomers or diastereoisomers. In particular, in formula (I) above two ring chiral centres are denoted with asterisks. It is to be understood that the invention includes both mixtures and separate individual isomers of the compounds of formula (I).

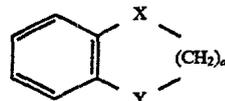
The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers thereof.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, benzene-sulphonate and p-toluenesulphonate salts. Compounds of the formula (I) can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

A particular group of compounds of the invention are those compounds of formula (I) in which R⁰ is hydrogen or halogen (e.g. fluorine), especially hydrogen.

Another particular group of compounds of the invention are those compounds of formula (I) in which R¹ represents hydrogen, C₁₋₄alkyl, haloC₁₋₄alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylmethyl, pyridylC₁₋₃alkyl, furylC₁₋₃alkyl or optionally substituted benzyl. Within this particular group of compounds, examples of C₁₋₄alkyl groups are methyl, ethyl, n-propyl, i-propyl and n-butyl. Examples of C₃₋₆cycloalkylmethyl groups are cyclopropylmethyl and cyclohexylmethyl. Examples of optionally substituted, benzyl groups include benzyl and halobenzyl (e.g. fluorobenzyl).

A further particular group of compounds of the invention are those compounds of formula (I) in which R² represents an optionally substituted benzene, thiophene, furan, pyridine or naphthalene ring or an optionally substituted bicyclic ring



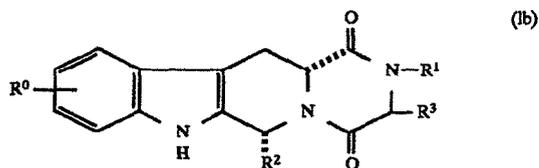
(where n is 1 or 2 and X and Y are each CH₂ or O). Within this particular group of compounds, examples of substituted benzene groups are benzene substituted by one of halogen (e.g. chlorine), hydroxy, C₁₋₃alkyl (e.g. methyl, ethyl or i-propyl), C₁₋₃alkoxy (e.g. methoxy or ethoxy), —CO₂R^b, halomethyl (e.g. trifluoromethyl), halomethoxy (e.g. trifluoromethoxy), cyano, nitro or NR^aR^b where R^a and R^b

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are each hydrogen or methyl or R^a is acetyl; or benzene substituted by dihalo (e.g. dichloro) or by C₁₋₃alkoxy (e.g. methoxy) and one of halogen (e.g. chlorine) and hydroxy. An example of a substituted thiophene ring is a halo (e.g. bromo) substituted thiophene ring.

A still further particular group of compounds of formula I are those wherein R² represents hydrogen or R¹ and R³ together represent a 3-membered alkyl chain.

A preferred group of compounds of the invention are the cis isomers of formula (I) represented by formula (Ib)



and mixtures thereof with their cis optical enantiomers, including racemic mixtures, and salts and solvates (e.g. hydrates) of these compounds in which R⁰ is hydrogen or halogen (e.g. fluorine), especially hydrogen and R¹, R² and R³ are as defined previously.

The single isomers represented by formula (Ib), i.e. the 6R, 12aR isomers, are particularly preferred.

Within the above definitions R¹ may preferably represent C₁₋₄alkyl (e.g. methyl, ethyl, i-propyl and n-butyl), C₃₋₆cycloalkyl (e.g. cyclopentyl) or C₃₋₆cycloalkylmethyl (e.g. cyclopropylmethyl).

R² may preferably represent a substituted benzene ring such as benzene substituted by C₁₋₃alkoxy (e.g. methoxy) or by C₁₋₃alkoxy (e.g. methoxy) and halogen (e.g. chlorine), particularly 4-methoxyphenyl or 3-chloro-4-methoxyphenyl, or R² may preferably represent 3,4-methylenedioxyphenyl.

It is to be understood that the present invention covers all appropriate combinations of particular and preferred groupings hereinabove.

Particular individual compounds of the invention include: Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-3,4-methylenedioxyphenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(5aR,12R,14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrazino[1'',2'':4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione;

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

A specific compound of the invention is:

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b] indole-1,4-dione;

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

It has been shown that compounds of the present invention are potent and selective inhibitors of cGMP specific PDE. Thus, compounds of formula (I) are of interest for use in therapy, specifically for the treatment of a variety of conditions where inhibition of cGMP specific PDE is thought to be beneficial.

As a consequence of the selective PDE V inhibition exhibited by compounds of the present invention, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic, vasodilatory, natriuretic and diuretic activities as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF), nitrovasodilators, atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and endothelium-dependent relaxing agents such as bradykinin, acetylcholine and 5-HT₁. The compounds of formula (I) therefore have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterised by disorders of gut motility (e.g. irritable bowel syndrome).

It will be appreciated that references herein to treatment extend to prophylaxis as well as treatment of established conditions.

It will also be appreciated that 'a compound of formula (I)', or a physiologically acceptable salt or solvate thereof can be administered as the raw compound, or as a pharmaceutical composition containing either entity.

There is thus provided as a further aspect of the invention a compound of formula (I) for use in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS).

According to another aspect of the invention, there is provided the use of a compound of formula (I) for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS).

In a further aspect, the invention provides a method of treating stable, unstable and variant (Prinzmetal) angina,

hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, (e.g. post-PTCA), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility (e.g. IBS) in a human or non-human animal body which comprises administering to said body a therapeutically effective amount of a compound with formula (I).

Compounds of the invention may be administered by any suitable route, for example by oral, buccal, sub-lingual, rectal, vaginal, nasal, topical or parenteral (including intravenous, intramuscular, subcutaneous and intracoronary) administration. Oral administration is generally preferred.

For administration to man in the curative or prophylactic treatment of the disorders identified above, oral dosages of a compound of formula (I) will generally be in the range of from 0.5800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 0.1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, a compound of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. Such liquid preparations may be prepared with pharmaceutically acceptable additives such as suspending agents (e.g. methylcellulose, a semi-synthetic glyceride such as witepsol or mixtures of glycerides such as a mixture of apricot kernel oil and PEG-6 esters or mixtures of PEG-8 and capryliccapric glycerides). A compound may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of the formula (I) together with a pharmaceutically acceptable diluent or carrier therefor.

There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a compound of formula (I), which process comprises mixing a compound of formula (I) together with a pharmaceutically acceptable diluent or carrier therefor.

A compound of formula (I) may also be used in combination with other therapeutic agents which may be useful in the treatment of the above-mentioned disease states. The

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invention thus provides, in another aspect, a combination of a compound of formula (I) together with another therapeutically active agent.

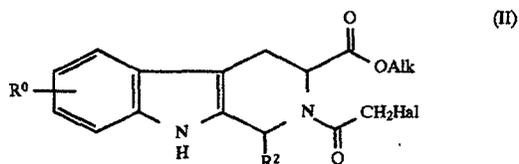
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination may also be administered either sequentially or simultaneously in separate pharmaceutical formulations.

Appropriate doses of known therapeutic agents for use in combination with a compound of formula (I) will be readily appreciated by those skilled in the art.

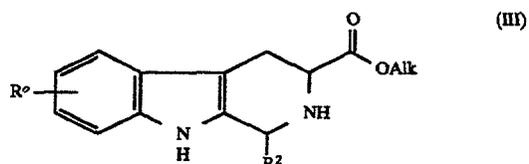
Compounds of formula (I) may be prepared by any suitable method known in the art or by the following processes which form part of the present invention. In the methods below R^0 , R^1 and R^2 are as defined in formula (I) above unless otherwise indicated.

Thus, a process (A) for preparing a compound of formula (I) wherein R^3 represents hydrogen comprises treating a compound of formula (II)



(in which Alk represents C_{1-6} alkyl, e.g. methyl or ethyl and Hal is a halogen atom, e.g. chlorine) with a primary amine R^1NH_2 in a suitable solvent such as an alcohol (e.g. methanol or ethanol) or a mixture of solvents, conveniently at a temperature of from $20^\circ C.$ to reflux (e.g. at about $50^\circ C.$).

A compound of formula (II) may conveniently be prepared by treating a compound of formula (III)



with a haloacetyl halide (e.g. chloroacetyl chloride) in a suitable solvent such as a halogenated hydrocarbon (e.g. trichloromethane or dichloromethane), or an ether (e.g. tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g. a trialkylamine such as triethylamine) or an alkali metal carbonate or bicarbonate (e.g. $NaHCO_3$). The reaction may conveniently be effected at a temperature of from $-20^\circ C.$ to $+20^\circ C.$ (e.g. at about $0^\circ C.$).

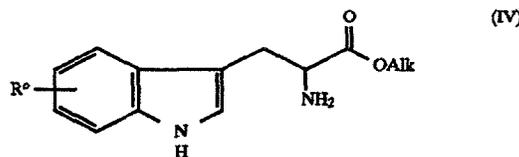
A compound of formula (I) may also be prepared from a compound of formula (III) in a two-step procedure via a compound of formula (II) isolated without purification.

Compounds of formula (I) may be prepared as individual enantiomers in two steps from the appropriate enantiomer of formula (III) or as mixtures (e.g. racemates) of either pairs of cis or trans isomers from the corresponding mixtures of either pairs of cis or trans isomers of formula (III).

Individual enantiomers of the compounds of the invention may be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using HPLC (high performance liquid chromatography) on a chiral column such as Hypersil naphthylurea.

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A compound of formula (III) may conveniently be prepared from a tryptophan alkyl ester of formula (IV)



(where Alk is as previously defined) or a salt thereof (e.g. the hydrochloride salt) according to either of the following procedures (a) and (b). Procedure (b) is only suitable for preparing cis isomers of formula (III) and may be particularly suitable for preparing individual cis enantiomers of formula (III) from D- or L-tryptophan alkyl esters as appropriate.

Procedure (a)

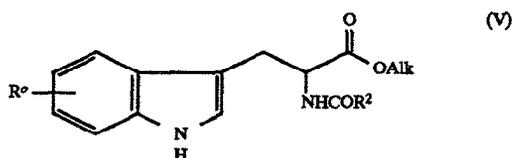
This comprises a Pictet-Spengler cyclisation between a compound of formula (IV) and an aldehyde R^2CHO . The reaction may conveniently be effected in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an aromatic hydrocarbon (e.g. toluene) in the presence of an acid such as trifluoroacetic acid. The reaction may conveniently be carried out at a temperature of from $-20^\circ C.$ to reflux to provide a compound of formula (III) in one step. The reaction may also be carried out in a solvent such as an aromatic hydrocarbon (e.g. benzene or toluene) under reflux, optionally using a Dean-Stark apparatus to trap the water produced.

The reaction provides a mixture of cis and trans isomers which may be either individual enantiomers or racemates of pairs of cis or trans isomers depending upon whether racemic or enantiomerically pure tryptophan alkyl ester was used as the starting material. Individual cis or trans enantiomers may conveniently be separated from mixtures thereof by fractional crystallisation or by chromatography (e.g. flash column chromatography) using appropriate solvents and eluents. Similarly, pairs of cis and trans isomers may be separated by chromatography (e.g. flash column chromatography) using appropriate eluents. An optically pure trans isomer may also be converted to an optically pure cis isomer using suitable epimerisation procedures. One such procedure comprises treating the trans isomer or a mixture (e.g. 1:1 mixture) of cis and trans isomers with methanolic or aqueous hydrogen chloride at a temperature of from $0^\circ C.$ to the refluxing temperature of the solution. The mixture may then be subjected to chromatography (e.g. flash column chromatography) to separate the resulting diastereoisomers, or in the procedure utilising aqueous hydrogen chloride the desired cis isomer precipitates out as the hydrochloride salt which may then be isolated by filtration.

Procedure (b)

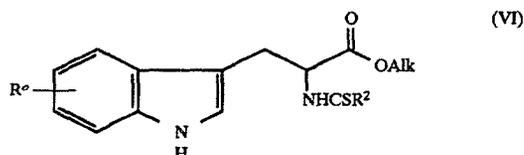
This comprises a four-step procedure from a compound of formula (IV) or a salt thereof (e.g. the hydrochloride salt). The procedure is particularly suitable for preparing a 1R, 3R isomer of formula (III) from a D-tryptophan alkyl ester of formula (IV) or a salt thereof (e.g. the hydrochloride salt). Thus, a first step (i) comprises treating a compound of formula (IV) with an acid halide R^2COHal (where Hal is as previously defined) in the presence of a base, e.g. an organic base such as a trialkylamine (for example triethylamine), to provide a compound of formula (V)

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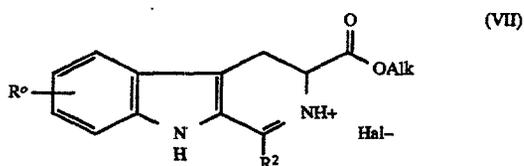


The reaction may be conveniently carried out in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an ether (e.g. tetrahydrofuran) and at a temperature of from -20°C . to $+40^{\circ}\text{C}$.

Step (ii) comprises treating a compound of formula (V) with an agent to convert the amide group to a thioamide group. Suitable sulfurating agents are well-known in the art. Thus, for example, the reaction may conveniently be effected by treating (V) with Lawesson's reagent. This reaction may conveniently be carried out in a suitable solvent such as an ether (e.g. dimethoxyethane) or an aromatic hydrocarbon (e.g. toluene) at an elevated temperature such as from 40°C . to 80°C . to provide a compound of formula (VI)



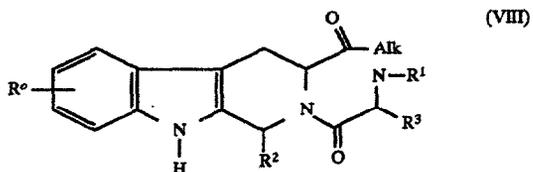
Step (iii) comprises treating a compound of formula (VI) with a suitable agent to provide a compound of formula (VII)



(where Hal is a halogen atom, e.g. iodine). The reaction may conveniently be effected by treating (VI) with an alkylating agent such as a methyl halide (e.g. methyl iodide) or an acylating agent such as an acetyl halide (e.g. acetyl chloride) in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) at an elevated temperature (e.g. under reflux).

In step (iv) the resulting iminium halide of formula (VII) may be treated with a reducing agent such as boron hydride, e.g. sodium borohydride, to provide the desired compound of formula (III). The reduction may conveniently be effected at a low temperature, e.g. within the range of -100°C . to 0°C ., in a suitable solvent such as an alcohol (e.g. methanol).

There is further provided by the present invention a process (B) for preparing a compound of formula (I), wherein R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain, which process (B) comprises cyclisation of a compound of formula (VIII)

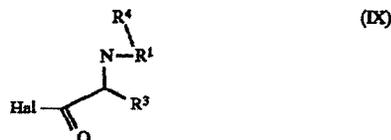


wherein Alk represents C_{1-6} alkyl and R^1 and R^3 together represent a 3- or 4-membered chain both as hereinbefore

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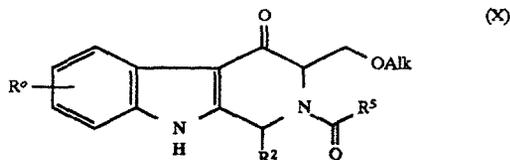
described. The cyclisation is suitably carried out in an organic solvent or solvents, such as an alcoholic solvent (e.g. methanol) and optionally an ether solvent such as tetrahydrofuran, and in the presence of a reducing agent, aptly a palladium catalyst, such as palladium on carbon.

Conveniently a compound of formula (VIII) is prepared by reaction of a compound of formula (III) as hereinbefore described with a compound of formula (IX)



wherein Hal represents a halogen atom as hereinbefore described, R^1 and R^3 together represent a 3- or 4-membered chain as hereinbefore described and R^4 represents a protecting group, suitably a benzyloxycarbonyl group or the like. Typically the reaction is carried out in a chlorinated organic solvent, such as dichloromethane, and a tertiary amine, such as triethylamine or the like.

According to a further aspect of the present invention, there is provided a process (C) for preparing a compound of formula (I) wherein R^3 represents C_{1-3} alkyl, which process comprises cyclisation of a compound of formula (X)



wherein Alk represents C_{1-6} alkyl as hereinbefore described and R^5 represents C_{2-5} alkyl, substituted at C_1 by a halogen atom, the halogen atom being as hereinbefore described. Suitably the cyclisation is achieved by reflux for many hours, such as 22 to 26 hours, in the presence of an ether solvent, such as tetrahydrofuran, and a suitable amine as hereinafter described in the accompanying examples.

Aptly a compound of formula (X) can be prepared from a compound of formula (III) by suitable acylation techniques, such as reaction with a C_{1-3} carboxylic acid, substituted at C_2 by a halogen atom in a halogenated organic solvent, such as dichloromethane.

Compounds of formula (I) may be converted to other compounds of formula (I). Thus, for example, when R^2 is a substituted benzene ring it may be necessary or desirable to prepare the suitably substituted compound of formula (I) subsequent to process (A), (B) or (C) as above. Examples of appropriate interconversions include nitro to amino or aralkyloxy to hydroxy by suitable reducing means (e.g. using a reducing agent such as SnCl_2 or a palladium catalyst, such as palladium-on-carbon), or amino to substituted amino such as acylamino or sulphonylamino using standard acylating or sulfonylating conditions. In the case where R^2 represents a substituted bicyclic system, suitable interconversion can involve removal of a substituent, such as by treatment with a palladium catalyst (e.g. palladium-on-carbon) whereby, for example, a benzyl substituent may be removed from a suitable bicyclic system.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I) which contain a basic centre may be prepared in a conventional manner. For example, a solution of the free base may be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt

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isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

Compounds of the invention may be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent.

Thus, according to a further aspect of the invention, we provide a process for preparing a compound of formula (I) or a salt or solvate (e.g. hydrate) thereof which comprises process (A), (B) or (C) as hereinbefore described followed by

- i) an interconversion step; and/or either
- ii) salt formation; or
- iii) solvate (e.g. hydrate) formation.

There is further provided by the present invention compounds of formulae (II), (VIII), (X) and further compounds of formulae (III), (V), (VI) and (VII), with the exception for compounds (III), (V), (VI) and (VII) wherein R^o is hydrogen, R² is phenyl and Alk is methyl.

The synthesis of the compounds of the invention and of the intermediates for use therein are illustrated by the following, non-limiting Examples. In the Examples section hereinafter the following abbreviations are used:

DMSO (dimethylsulphoxide), MeOH (methanol), EtOH (ethanol), DMF (dimethylformamide), EtOAc (ethyl acetate) and THF (tetrahydrofuran).

INTERMEDIATES 1 AND 2

Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, Cis and Trans isomers

To a stirred solution of racemic tryptophan methyl ester (13 g) and piperonal (9.7 g) in anhydrous CH₂Cl₂ (300 mL) cooled at 0° C. was added dropwise trifluoroacetic acid (9 mL) and the solution was allowed to react at ambient temperature. After 4 days, the yellow solution was diluted with CH₂Cl₂ (100 mL), washed with a saturated aqueous solution of NaHCO₃, then with water and dried over Na₂SO₄. The organic layer was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography eluting with CH₂Cl₂/MeOH (99/1) to give first Intermediate 1, the cis isomer (6.5 g) m.p. 90–93° C. followed by Intermediate 2, the trans isomer (6.4 g) m.p.:170° C.

The following compounds were obtained in a similar manner:

INTERMEDIATES 3 AND 4

Methyl 1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-methoxybenzaldehyde gave Intermediate 3, the cis isomer as white crystals

m.p.:142° C. and Intermediate 4, the trans isomer as white crystals m.p.:209°–210° C.

INTERMEDIATE 5

Methyl 1,2,3,4-tetrahydro-1-(3-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

The same method but starting from racemic tryptophan methyl ester and 3-methoxybenzaldehyde gave the title compound as white crystals m.p.:146° C.

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INTERMEDIATES 6 AND 7

Methyl 1,2,3,4-tetrahydro-1-(4-ethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-ethoxybenzaldehyde gave Intermediate 6, the cis isomer as white crystals m.p.:180° C. and Intermediate 7, the trans isomer as white crystals m.p.:196°–198° C.

INTERMEDIATES 8 AND 9

Methyl 1,2,3,4-tetrahydro-1-(2,3-dihydrobenzo[b]furan-5-yl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 2,3-dihydrobenzo[b]furan-5-carboxaldehyde gave Intermediate 8, the cis isomer as white crystals m.p.:106°–109° C. and Intermediate 9, the trans isomer as white crystals m.p.:219°–222° C.

INTERMEDIATES 10 AND 11

Methyl 1,2,3,4-tetrahydro-1-(3,4-ethylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 1,4-benzodioxan-6-carboxaldehyde gave Intermediate 10, the cis isomer as white crystals m.p.:104°–106° C. and Intermediate 11, the trans isomer as white crystals m.p.:207°–209° C.

INTERMEDIATE 12

Methyl 1,2,3,4-tetrahydro-1-(2-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 2-chlorobenzaldehyde gave the title compound as white crystals m.p.:154° C.

INTERMEDIATES 13 AND 14

Methyl 1,2,3,4-tetrahydro-1-(4-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-chlorobenzaldehyde gave Intermediate 13, the cis isomer as white crystals m.p.:208°–209° C. and Intermediate 14, the trans isomer as white crystals m.p.:108°–109° C.

INTERMEDIATES 15 AND 16

Methyl 1,2,3,4-tetrahydro-1-(3,4-dichlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 3,4-dichlorobenzaldehyde gave Intermediate 15, the cis isomer as a white solid ¹H NMR (CDCl₃)_δ (ppm):7.8–7 (m, 8H, H aromatic); 5.15 (brs, 1H, H-1); 3.9–3.8 (dd, 1H, H-3) 3.7 (s, 3H, CO₂CH₃); 3.2–3.1 (ddd, 1H, H-4) 2.9 (m, 1H-4); 2.4 (brs, 1H, NH) and Intermediate 16, the trans isomer as a white solid m.p. 204° C.

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INTERMEDIATE 17

Methyl 1,2,3,4-tetrahydro-1-(1,2,3,4-tetrahydro-6-naphthyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

The same method but starting from racemic tryptophan methyl ester and 1,2,3,4-tetrahydronaphthyl-6-carboxaldehyde gave the title compound as a white solid $^1\text{H NMR}$ (CDCl_3) δ (ppm): 7.7-7(m, 8H, H aromatic); 5.2 (s, 1H, H-1); 4.0 (dd, 1H, H-3); 3.8 (s, 3H, CO_2CH_3); 3.2 (m, 1H, H-4); 3.0 (m, 1H, H-4); 2.7 (m, 4H, CH_2Ar); 1.7 (s, 4H, $\text{CH}_2\text{CH}_2\text{Ar}$).

INTERMEDIATES 18 AND 19

Methyl 1,2,3,4-tetrahydro-1-(2-naphthyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 2-naphthaldehyde gave Intermediate 18, the cis isomer as a white solid $^1\text{H NMR}$ (CDCl_3) δ (ppm): 8-6.9 (m, 12H, H aromatic); 5.4 (s, 1H, H-1); 3.95 (dd, 1H, H-3); 3.7 (s, 3H, CO_2CH_3); 3.2 (ddd, 1H, H-4); 3 (m, 1H, H-4); 2.5 (brs, 1H, NH) and Intermediate 19, the trans isomer as a white solid (0.6 g) m.p.: 11 $^\circ\text{C}$.

INTERMEDIATES 20 AND 21

Methyl 1,2,3,4-tetrahydro-1-(2-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans is

The same method but starting from racemic tryptophan methyl ester and 2-thiophenecarboxaldehyde gave Intermediate 20, the cis isomer as a pale yellow solid m.p.: 134 $^\circ$ -137 $^\circ\text{C}$. and Intermediate 21, the trans isomer as white crystals m.p.: 169 $^\circ\text{C}$.

INTERMEDIATES 22 AND 23

Ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans iso

The same method but starting from racemic tryptophan ethyl ester and 3-thiophenecarboxaldehyde gave Intermediate 22, the cis isomer as white crystals m.p.: 130 $^\circ\text{C}$. and Intermediate 23, the trans isomer as white crystals m.p.: 182 $^\circ$ -184 $^\circ\text{C}$.

INTERMEDIATES 24 AND 25

Methyl 1,2,3,4-tetrahydro-1-(5-bromo-2-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 5-bromo-2-thiophenecarboxaldehyde gave Intermediate 24, the cis isomer as a cream solid m.p.: 130 $^\circ\text{C}$. and Intermediate 25, the trans isomer as a cream solid m.p.: 205 $^\circ\text{C}$.

INTERMEDIATES 26 AND 27

Methyl 1,2,3,4-tetrahydro-1-(4-bromo-2-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-bromo-2-thiophenecarboxaldehyde gave Intermediate 26, the cis isomer as a cream solid m.p.: 200 $^\circ\text{C}$. and Intermediate 27, the trans isomer as a cream solid m.p.: 120 $^\circ\text{C}$.

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INTERMEDIATE 28

Methyl 1,2,3,4-tetrahydro-1-(3-furyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 3-furaldehyde gave the title compound as a yellow solid m.p.: 130 $^\circ\text{C}$.

INTERMEDIATES 29 AND 30

Ethyl 1,2,3,4-tetrahydro-1-(5-methyl-2-furyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 5-methylfurfural gave Intermediate 29, the cis isomer as a oily compound $^1\text{H NMR}$ (CDCl_3) δ (ppm): 7.7 (brs, 1H, NH indole); 7.5 (d, 1H, H aromatic); 7.25-6.9 (m, 3H, H aromatic); 6.15 (d, 1H, H aromatic); 5.85 (m, 1H, H aromatic); 5.25 (brs, 1H, H-1); 4.2 (q, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$); 3.8 (dd, 1H, H-3); 3.2-2.8 (m, 2H, H-4); 2.2 (s, 3H, CH_3); 1.25 (t, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$) and Intermediate 30, the trans isomer as a cream solid m.p.: 152 $^\circ\text{C}$.

INTERMEDIATES 31 AND 32

Ethyl 1,2,3,4-tetrahydro-1-(4-methylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and p-tolualdehyde gave Intermediate 31, the cis isomer as white crystals m.p.: 148 $^\circ\text{C}$. and Intermediate 32, the trans isomer as white crystals m.p.: 180 $^\circ\text{C}$.

INTERMEDIATES 33 AND 34

Methyl 1,2,3,4-tetrahydro-1-(3-methylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and m-tolualdehyde gave Intermediate 33, the cis isomer as white crystals $^1\text{H NMR}$ (CDCl_3) δ (ppm): 7.6-7 (m, 9H, H aromatic); 5.2 (brs, 1H, H-1); 4-3.9 (dd, 1H, H-3); 3.8 (s, 3H, CO_2CH_3); 3.2-3.1 (ddd, 1H, H-4); 3 (m, 1H, H-4); 2.35 (s, 3H, CH_3); 1.7 (brs, 1H, NH) and Intermediate 34, the trans isomer as a white solid m.p.: 175 $^\circ\text{C}$.

INTERMEDIATES 35 AND 36

Methyl 1,2,3,4-tetrahydro-1-(4-trifluoromethylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-trifluoromethylbenzaldehyde gave Intermediate 35, the cis isomer as pale yellow crystals m.p.: 190 $^\circ\text{C}$. and Intermediate 36, the trans isomer as pale yellow crystals m.p.: 203 $^\circ\text{C}$.

INTERMEDIATES 37 AND 38

Ethyl 1,2,3,4-tetrahydro-1-(4-cyanophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 4-cyanobenzaldehyde gave Intermediate 37,

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the cis isomer as white crystals m.p.:200° C. and Intermediate 38, the trans isomer as white crystals m.p.:156° C.

INTERMEDIATE 39

Methyl 1,2,3,4-tetrahydro-1-(4-hydroxyphenyl)-9H-pyrido[3,4b]indole-3-carboxylate, cis isomer

The same method but starting from racemic tryptophan ethyl ester and 4-hydroxybenzaldehyde gave the title compound as pale yellow crystals ¹H NMR (DMSO)δ(ppm):10.3 (s, 1H, NH-indole) 9.4 (s, 1H, OH); 7.8-7.5 (m, 8H, H aromatic); 5.1 (brs, 1H, H-1); 3.9 (m, 1H, H-3); 3.75 (s, 3H, CO₂CH₃) 3.1 (m, 1H, H4); 2.8 (m, 1H, H-4).

INTERMEDIATE 40

Methyl 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

The same method but starting from racemic tryptophan methyl ester and 3-hydroxy-4-methoxybenzaldehyde gave the title compound as a yellow solid m.p.:140°-148° C.

INTERMEDIATE 41

Methyl 1,2,3,4-tetrahydro-1-(4-hydroxy-3-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

The same method but starting from racemic tryptophan methyl ester and 4-hydroxy-3-methoxybenzaldehyde gave the title compound as a cream solid m.p.:195° C.

INTERMEDIATE 42

Methyl 1,2,3,4-tetrahydro-1-(4-ethylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 4-ethylbenzaldehyde gave the cis and trans isomer of the title compound. Cis isomer:white solid ¹H NMR (CDCl₃)δ(ppm):7.65-7.1 (m, 9H, H aromatic); 5.25 (brs, 1H, H-1); 4 (dd, 1H, H-3); 3.9 (s, 3H, CO₂CH₃); 3.4 (ddd, 1H, H-4); 3.1 (m, 1H, H-4); 2.7 (q, 2H, CH₂CH₃) 1.4 (t, 3H, CH₂CH₃). Trans isomer:white solid m.p.:187° C.

INTERMEDIATES 43 AND 44

Methyl 1,2,3,4-tetrahydro-1-(4-isopropylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 4-isopropylbenzaldehyde gave Intermediate 43, the cis isomer as a white solid ¹H NMR (DMSO)δ(ppm):10.15 (s, 1H, NH indole); 7.3-6.7 (m, 8H, H aromatic); 5 (brs, 1H, H-1); 3.6 (m, 1H, H-3); 3.5 (s, 3H, CO₂CH₃); 2.95-2.5 (m, 3H, H-4+CH-(Me)₂) 2.4 (brs, 1H, NH); 1 (d, 6H, 2xCH₂) and Intermediate 44, the isomer as a white solid m.p.:189° C.

INTERMEDIATES 45 AND 46

Ethyl 1,2,3,4-tetrahydro-1-(4-nitrophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 4-nitrobenzaldehyde gave Intermediate 45,

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the cis isomer as yellow crystals m.p.:168° C. and Intermediate 46, the trans isomer as yellow crystals m.p.:195° C.

INTERMEDIATE 47

Ethyl 1,2,3,4-tetrahydro-1-(4-dimethylaminophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 4-dimethylaminobenzaldehyde gave the title compound as white crystals m.p.:170° C.

INTERMEDIATES 48 AND 49

Ethyl 1,2,3,4-tetrahydro-1-(3-pyridyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans iso

The same method but starting from racemic tryptophan ethyl ester and 3-pyridinecarboxaldehyde gave Intermediate 48, the cis isomer as pale yellow crystals m.p.:230°-232° C. and Intermediate 49, the trans isomer as white crystals m.p.:210°-214° C.

INTERMEDIATES 50 AND 51

Methyl 1,2,3,4 tetrahydro-6-fluoro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic 5-fluorotryptophan methyl ester and piperonal gave Intermediate 50, the cis isomer as a cream solid m.p.:60° C. and Intermediate 51, the trans isomer as a cream solid m.p.:213° C.

INTERMEDIATES 52 AND 53

Methyl 1,2,3,4-tetrahydro-6-fluoro-1-(4-methoxyphenyl)-9H-pyrido[3,4b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic 5-fluorotryptophan methyl ester and 4-methoxybenzaldehyde gave Intermediate 52, the cis isomer as a solid ¹H NMR (CDCl₃) δ(ppm):7.4-6.8 (m, 8H, H aromatic); 5.15 (brs, 1H, H-1); 3.9 (dd, 1H, H-3) 3.8 (s, 3H, CO₂CH₃); 3.2-2.9 (m, 2H, H-4) and Intermediate 53, the trans isomer as a solid m.p.:197° C.

INTERMEDIATES 54 AND 55

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

To a stirred solution of D-tryptophan methyl ester (11 g) and piperonal (7.9 g) in anhydrous CH₂Cl₂ (400 mL) cooled at 0° C. was added dropwise trifluoroacetic acid (7.7 mL) and the solution was allowed to react at ambient temperature. After 4 days, the yellow solution was diluted with CH₂Cl₂ (200 mL) and washed with a saturated aqueous solution of NaHCO₃, then with water (3x200 mL) and dried over Na₂SO₄. The organic layer was evaporated under reduced pressure and the residue was purified by flash chromatography eluting with dichloromethane/ethyl acetate (97/3) to give first Intermediate 54, the cis isomer (6.5 g) m.p.:154° C. followed by Intermediate 55, the trans isomer (8.4 g) m.p.: 188° C.

The following compounds were obtained in a similar manner:

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INTERMEDIATE 56

(1S,3S) Methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1R, 3S) methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

The same method but starting from L-tryptophan methyl ester and piperonal gave the cis and trans isomers of the title compound.

Cis isomer:white crystals m.p.:154° C.

Trans isomer:white crystals m.p.:187°-189° C.

INTERMEDIATES 57 AND 58

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

The same method but starting from D-tryptophan methyl ester and 4-methoxybenzaldehyde gave Intermediate 57, the cis isomer as white crystals m.p.:124°-125° C. and Intermediate 58, trans isomer as white crystals m.p.: 219-222° C.

INTERMEDIATES 59 AND 60

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3-chloro-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3-chloro-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

The same method, but starting from D-tryptophan methyl ester and 3-chloro-4-methoxybenzaldehyde gave Intermediate 59, the cis isomer isolated as the hydrochloride salt as white crystals m.p.:200° C. and Intermediate 60, the trans isomer as white crystals m.p.:164° C.

INTERMEDIATES 61 AND 62

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(2,3-dihydrobenzo[b]furan-5-yl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(5-(2,3-dihydrobenzo[b]furan))-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

The same method but starting from D-tryptophan methyl ester and 2,3-dihydrobenzo[b]furan-5-carboxaldehyde gave Intermediate 61, the cis isomer as white crystals m.p.:282° C. and Intermediate 62, the trans isomer as white crystals m.p.:204° C.

INTERMEDIATES 63 AND 64

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-indanyl)-9H-pyrido[3,4-b]indole-3-carboxylate cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(5-indanyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

The same method but starting from D-tryptophan methyl ester and indan-5-carboxaldehyde gave Intermediate 63, the cis isomer as white crystals m.p.:130°-131° C. and Intermediate 64, the trans isomer as white crystals m.p.:196° C.

INTERMEDIATE 65

Ethyl 1,2,3,4-tetrahydro-1-(4-trifluoromethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan ethyl ester and 4-trifluoromethoxybenzaldehyde gave cis and trans isomers of the title compound.

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Cis isomer:white crystals m.p.:88° C.

Trans isomer:white crystals m.p.:152° C.

INTERMEDIATE 66

Methyl 1,2,3,4-tetrahydro-1-(5-methyl-2-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic tryptophan methyl ester and 5-methyl-2-thiophenecarboxaldehyde gave the cis and trans isomers of the title compound.

Cis isomer:oily compound ¹H NMR (CDCl₃)δ(ppm):8.4 (brs, 1H, NH-indole); 7.7-6.6 (m, 6H, H aromatic); 5.5 (brs, 1H, H-1); 3.9 (dd, 1H, H-3); 3.85 (s, 3H, CO₂CH₃); 3.3-2.9 (m, 2H, H-4); 2.5 (s, 3H, CH₃).

Trans isomer:white crystals m.p.:194° C.

INTERMEDIATES 67 AND 68

(1S,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate and (1R, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

To a stirred solution of D-tryptophan methyl ester (obtained by treating the corresponding hydrochloride salt in water with saturated aqueous NaHCO₃ solution and extraction with CH₂Cl₂) (25.7 g) and piperonal (19.4 g) in anhydrous dichloromethane (700 ml) cooled to 0° C. was added dropwise trifluoroacetic acid (18.1 ml) and the solution was allowed to react at 4° C. After 5 days, the yellow solution was diluted with dichloromethane (500 ml). The organic layer was washed with a saturated aqueous solution of NaHCO₃, then with water (3x500 ml) until the pH was neutral and dried over Na₂SO₄. The organic layer was evaporated under reduced pressure to a volume of about 500 ml. The trans-isomer, which crystallised, was filtered and the filtrate was reduced to 200 ml. Another fraction of the trans-isomer crystallised. The fractions of trans-isomer were combined to give the (1S, 3R) isomer, Intermediate 67, as white crystals (11.4 g).

mp:188° C.

[α]_D²⁰ = +32.4° (c=1.03, CHCl₃).

The filtrate containing mainly the cis-isomer was reduced to 100 ml and isopropyl ether (200 ml) was added. Upon cooling, the (1R, 3R) isomer, Intermediate 68, crystallised as a white solid (17.4 g).

mp:154°-155° C.

[α]_D²⁰ = +24.4° (c=1.03, CHCl₃).

INTERMEDIATE 69

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Method A

Intermediate 67 (5.0 g) was dissolved in methanol (150 ml). Hydrogen chloride was bubbled into the solution for several minutes at 0° C. and the resulting yellow solution was refluxed for 24 hours. The solvent was removed under reduced pressure and the residue was basified with a saturated aqueous solution of NaHCO₃ and extracted with dichloromethane. The organic layer was washed with water, dried over Na₂SO₄ and purified by flash chromatography eluting with dichloromethane/methanol (99/1) to give the

title compound (2.3 g) corresponding to an authentic sample of Intermediate 68.

Method B

Intermediate 67 (25 g) was heated in 1N hydrochloric acid (78.5 ml) and water (400 ml) at 60° C. for 36 hours. From the initial pale yellow solution, a white solid precipitated. The mixture was then allowed to cool to 0° C. and the solid filtered. The solid was then washed with diisopropyl ether (3x200 ml) and dried to give the hydrochloride salt of the title compound (20 g) as a white solid. mp (dec.):209°-212° C.

Method C

A 1:1 mixture of the cis and trans isomers of Intermediates 54 and 55 (2 g) was heated in 1N hydrochloric acid (6.8 ml) and water (15 ml) at 50° C. for 72 hours. A similar work-up as described in Method B above gave the hydrochloride salt of the title compound (1.7 g) as a white solid.

INTERMEDIATE 70

(R)-N^α-(3,4-Methylenedioxyphenylcarbonyl)-tryptophan methyl ester

To a suspension of D-tryptophan methyl ester hydrochloride (10.2 g) in anhydrous CH₂Cl₂ (150 ml) cooled at 0° C. was added dropwise triethylamine (12.3 ml). To the resulting solution solid piperonyl chloride (8.16 g) was added portionwise at the same temperature, and the mixture was stirred at room temperature for 2 h. The mixture was washed successively with water, 0.5N hydrochloric acid, water, a saturated aqueous solution of NaHCO₃ and again with water. After drying over Na₂SO₄ and evaporation of the solvent under reduced pressure, the resulting oil on trituration from hot cyclohexane afforded the title compound as a white solid (14.7 g).

mp:123°-124° C.

[α]_D^{20°} = -84.4° (c=1.04, CHCl₃).

INTERMEDIATE 71

(R)-N^α-(3,4-Methylenedioxyphenylthiocarbonyl)-tryptophan methyl ester

A mixture of Intermediate 70 (14 g) and Lawesson's reagent (9.28 g) in dimethoxyethane (280 ml) was heated at 60° C. under N₂ for 16 hours with stirring. The reaction mixture was evaporated to dryness and the resulting oil was dissolved in ethyl acetate, then washed successively with an aqueous saturated solution of NaHCO₃ and water and dried over Na₂SO₄. The oily residue obtained after evaporation under reduced pressure gave, on trituration from cyclohexane, a yellow powder which was filtered and washed with cooled methanol to afford the title compound (9.74 g).

mp:129°-130° C.

[α]_D^{20°} = -186.8° (c=1.14, CHCl₃).

INTERMEDIATE 72

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

A solution of Intermediate 71 (9 g) and methyl iodide (10 ml) in anhydrous dichloromethane (200 ml) was heated at reflux under an argon atmosphere with protection from light. After 24 hours, the solvent was removed under reduced pressure to give an orange oil which on trituration from

hexane gave a solid which was washed with ether and used without further purification in the next step. This compound (13.11 g) was dissolved in methanol (250 ml) and the solution was cooled to -78° C. NaBH₄ (0.99 g) was then added by portions and the mixture was stirred at the same temperature for 1 hour. The reaction was quenched by addition of acetone (10 ml) and the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with water and then with brine and dried over Na₂SO₄. After evaporation of the solvent, the orange oil gave on trituration from a hot mixture of diethyl ether/cyclohexane an orange powder which was recrystallised from diethyl ether/pentane to afford the title compound as a pale yellow solid (5.15 g) corresponding to an authentic sample of Intermediate 68.

INTERMEDIATE 73

(1R,3R)-Methyl 1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Method A

To a stirred solution of Intermediate 72 (9.7 g) and NaHCO₃ (2.79 g) in anhydrous CHCl₃ (200 ml) was added dropwise chloroacetyl chloride (5.3 ml) at 0° C. under N₂. The resulting mixture was stirred for 1 hour at the same temperature and diluted with CHCl₃ (100 ml). Water (100 ml) was then added dropwise with stirring to the mixture, followed by a saturated aqueous solution of NaHCO₃. The organic layer was washed with water until neutrality and dried over Na₂SO₄. After evaporation of the solvent under reduced pressure, the oily compound obtained was crystallised from ether to give the title compound as a pale yellow solid (9.95 g).

mp:233° C.

[α]_D^{20°} = -125.4° (c=1.17, CHCl₃).

Method B

Chloroacetyl chloride (4 ml) was added dropwise to a solution of Intermediate 72 (16.1 g) and triethylamine (7 ml) in anhydrous CH₂Cl₂ (200 ml) at 0° C. under N₂. The solution was stirred at 0° C. for 30 minutes, then diluted with CH₂Cl₂ (300 ml). The solution was washed with water (200 ml), a saturated aqueous solution of NaHCO₃ (300 ml) and brine (400 ml). After drying over Na₂SO₄ and evaporation under reduced pressure, the resulting solid was washed with ether (300 ml) to give the title compound as a pale yellow solid (18.3 g).

INTERMEDIATE 74

Methyl 1,2,3,4-tetrahydro-6-methyl-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

The cis and trans isomers of the title compound were prepared using the method described in Intermediate 1 but starting from racemic 5-methyl-tryptophan methyl ester and piperonal.

Cis isomer: yellow solid m.p.:85° C.

Trans isomer: yellow solid m.p.:185° C.

INTERMEDIATES 75 AND 76

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(7-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazinyloxy)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-

Methyl 1,2,3,4-tetrahydro-1-(7-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazinyloxy)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

The same method, as described for intermediates 54 and 55, but starting from D-tryptophan methyl ester and

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4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxaldehyde gave Intermediate 75 the cis isomer as an oily compound $^1\text{H NMR}$ (CDCl_3) δ (ppm):7.6–7.1 (m, 5H); 6.9–6.6 (m, 3H); 5.15 (br s, 1H); 4.3 (t, 2H); 4 (dd, 1H); 3.8 (s, 3H); 3.3 (t, 2H); 3.3–2.95 (m, 2H); 2.9 (s, 3H); 1.6 (br s) and intermediate 76, the trans isomer as white crystals m.p.:119°–121° C.

INTERMEDIATE 77

Methyl 1,2,3,4-tetrahydro-1-(5-(N-benzylindolyl))-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of (1R, 3R) and (1S, 3R) isomers

The same method, as described for intermediates 54 and 55, but starting from D-tryptophan methyl ester and N-benzylindoline-5-carboxaldehyde gave intermediate 77 as an oily compound.

INTERMEDIATES 78 AND 79

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(4-carbomethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(4-carbomethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

The same method, as described for intermediates 54 and 55, but starting from D-tryptophan methyl ester and methyl 4-formylbenzoate gave Intermediate 78, the cis isomer as white crystals m.p.:157°–160° C. and Intermediate 79, the trans isomer as pale yellow crystals m.p.:124°–126° C.

INTERMEDIATE 80

(1R,3R)-Methyl 1,2,3,4-tetrahydro-2-[2-(benzyloxycarbonyl)-S-propyl]-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

A solution of N-(benzyloxycarbonyl)-D-proline acid chloride (0.64 g, 2.4 mmol) in anhydrous dichloromethane (10 mL) was added dropwise to a stirred solution of intermediate 54 (0.7 g, 2 mmol) and triethylamine (0.33 mL, 2.4 mmol) in dichloromethane (15 mL) at -10° C. The mixture was stirred for 2 h at -10° C. after which it was diluted with dichloromethane (50 mL), washed with hydrochloric acid (1N), water, a saturated solution of NaHCO_3 , a saturated NaCl solution and dried over Na_2SO_4 . Evaporation of the solvent and recrystallisation of the crude product from methanol gave the title compound as pale yellow crystals (0.75 g) m.p.:268°–270° C.

INTERMEDIATE 81

(1R,3R)-Methyl 1,2,3,4-tetrahydro-2-[2-(benzyloxycarbonyl)-S-propyl]-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

A solution of N-(benzyloxycarbonyl)-L-proline acid chloride (0.86 g, 3.2 mmol) in anhydrous dichloromethane (10 mL) was added dropwise to a stirred solution of intermediate 54 (0.91 g, 2.6 mmol) and triethylamine (0.44 mL, 3.2 mmol) in dichloromethane (20 mL) at -10° C. The mixture was stirred for 2 hours at -10° C. after which it was diluted with dichloromethane (60 mL), washed with hydrochloric acid (1N), water, a saturated solution of NaHCO_3 , a saturated NaCl solution and dried over Na_2SO_4 . Evaporation of the solvent and recrystallisation of the crude product from

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methanol/water gave the title compound as pale yellow crystals (0.8 g) m.p.:115°–120° C.

INTERMEDIATE 82

(1R,3R)-Methyl 1,2,3,4-tetrahydro-2-(2-chloropropionyl)-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

To a solution of (S)-(-)-2-chloropropionic acid (87 μL , 1 mmol) in anhydrous dichloromethane (15 mL), was added dicyclohexylcarbodiimide (0.23 g, 1.1 mmol). Intermediate 54 (0.35 g, 1 mmol) was then added and the mixture was stirred at room temperature for 20 hours. The formed precipitate of dicyclohexylurea was removed by filtration, the filtrate was evaporated in vacuo and the crude product was purified by flash chromatography eluting with toluene/ethyl acetate:95/5. The oily compound obtained was then crystallised from ether/hexane to give the title compound as pale yellow crystals (0.31 g) m.p.:125°–127° C.

INTERMEDIATE 83

(1R,3R)-Methyl 1,2,3,4-tetrahydro-2-(2-chloropropionyl)-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

To a solution of (R)-(+)-2-chloropropionic acid (191 μL , 2.2 mmol) in anhydrous dichloromethane (30 mL), was added dicyclohexylcarbodiimide (0.45 g, 2.2 mmol). Intermediate 54 (0.7 g, 2 mmol) was then added and the mixture was stirred at room temperature for 20 hours. The formed precipitate of dicyclohexylurea was removed by filtration, the filtrate was evaporated in vacuo and the crude product was purified by flash chromatography eluting with toluene/ethyl acetate:95/5. The oily compound obtained was then crystallised from ether/hexane to give the title compound as pale yellow crystals (0.74 g) m.p.:126°–128° C.

INTERMEDIATES 84 AND 85

(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-dibenzoyloxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-dibenzoyloxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

The same method as described for intermediates 54 and 55 but starting from D-tryptophan methyl ester and 3,4-dibenzoyloxybenzaldehyde gave intermediate 84, the cis isomer as an oily compound $^1\text{H NMR}$ (CDCl_3) δ (ppm):7.5–6.95 (m, 15H); 6.85 (s, 1H); 6.75 (s, 2H); 5.1 (s, 2H); 5 (br s, 1H); 4.95 (d, 2H 3.85 (dd, 1H); 3.7 (s, 3H); 3.2–2.8 (m, 2H); 2.3 (br s, 1H) and intermediate 85, the trans isomer as an oily compound $^1\text{H NMR}$ (CDCl_3) δ (ppm) 7.6–7 (m, 15H); 6.9–6.7 (m, 3H); 5.2 (br s, 1H); 5.1 (s, 2H); 5 (s, 2H); 3.8 (t, 1H); 3.65 (s, 3H); 3.3–3 (m, 2H); 2.25 (br s, 1H).

INTERMEDIATE 86

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-dibenzoyloxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from intermediate 84 and methylamine gave, after recrystallisation from dichloromethane/ether, the title compound as white crystals m.p.:158°–160° C., $[\alpha]_D^{20} = +11.7^\circ$ ($c = 1.23$; CHCl_3).

INTERMEDIATE 87

Methyl 1,2,3,4-tetrahydro-1-(5-(2-methylisindolyl))-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of (1R, 3R) and (1S, 3R) isomers

The same method, as described for intermediates 54 and 55, but starting from D-tryptophan methyl ester and

N-methylisindoline-5 carboxaldehyde gave intermediate 87 as an oily compound.

EXAMPLE 1

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

a) To a stirred solution of intermediate 1 (2 g) and NaHCO₃ (0.6 g) in anhydrous CHCl₃ (40 mL) was added dropwise chloroacetyl chloride (1.1 mL) at 0° C. The resulting mixture was stirred for 1 hour at the same temperature and diluted with CHCl₃. Water (20 mL) was then added dropwise with stirring to the mixture, followed by a saturated solution of NaHCO₃. The organic layer was washed with water until neutrality and dried over Na₂SO₄. After evaporation of the solvent under reduced pressure, cis-methyl 1,2,3,4-tetrahydro-2-chloroacetyl-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate was obtained as an oil which was crystallised from ether (2 g, m.p.:215°-218° C.) and was used without further purification in the next step.

b) To a stirred suspension of the chloroacetyl intermediate (0.34 g) in MeOH (20 mL) was added at ambient temperature a solution of methylamine (33% in EtOH) (0.37 mL) and the resulting mixture was heated at 50° C. under N₂ for 14 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (50 mL). After washing with water (3x30 mL), drying over Na₂SO₄ and evaporating to dryness, the residue was purified by flash chromatography eluting with CH₂Cl₂/MeOH (99/1) and recrystallised from MeOH to give the title compound as white crystals (0.19 g) m.p.:253°-255° C.

Analysis for C₂₂H₁₉N₃O₄: Calculated:C,67.86;H,4.92;N,10.79; Found:C,67.53;H,4.99;N,10.62%.

The following compounds were obtained in a similar manner:

EXAMPLE 2

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-10-fluoro-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 52 gave, after recrystallisation from ethanol, the title compound as white crystals

m.p.:182° C.

Analysis for C₂₅H₂₆FN₃O₃ (0.1 H₂O): Calculated:C,68.67;H,6.04;N,9.61; Found:C,68.38;H,6.11;N,9.53%.

EXAMPLE 3

Trans-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 2 gave, after recrystallisation from toluene, the title compound as white crystals

m.p.:301°-303° C.

Analysis for C₂₂H₁₉N₃O₄: Calculated:C,67.86;H,4.92;N,10.79; Found:C,67.98;H,4.98;N,10.73%.

EXAMPLE 4

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from ammonia and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals

m.p.:283°-285° C.

Analysis for C₂₁H₁₇N₃O₄: Calculated:C,67.19;H,4.56;N,11.19; Found:C,67.04;H,4.49;N,11.10%.

EXAMPLE 5

Cis-2,3,6,7,12,12a-hexahydro-10-fluoro-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 2,2,2-trifluoroethylamine and intermediate 52 gave, after recrystallisation from ethanol/diisopropyl ether, the title compound as white crystals m.p.:190° C.

Analysis for C₂₃H₁₉F₄N₃O₃: Calculated:C, 59.87; H, 4.15; N, 9.11; Found:C, 59.81; H, 4.18; N, 9.21%.

EXAMPLE 6

Cis-2,3,6,7,12,12a-hexahydro-10-fluoro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 50 gave, after recrystallisation from ethanol, the title compound as white crystals

m.p.:292° C.

Analysis for C₂₂H₁₈FN₃O₄: Calculated:C, 64.86; H, 4.45; N, 10.31; Found:C, 64.66; H, 4.60; N, 10.21%.

EXAMPLE 7

(6R,12aS)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and the trans isomer of intermediate 56 gave, after recrystallisation from toluene, the title compound as white crystals m.p.:287°-289° C.

Analysis for C₂₂H₁₉N₃O₄ (0.25 toluene): Calculated:C, 69.16;H,5.13;N,10.19; Found:C,69.09;H,5.14;N,10.19%. [α]_D^{20°} = -293.4° (C=1.28; CHCl₃).

EXAMPLE 8

(6S,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 55 gave, after recrystallisation from toluene, the title compound as white crystals

m.p.:287° C.

Analysis for C₂₂H₁₉N₃O₄ (0.3 toluene): Calculated:C, 69.41; H, 5.17; N, 10.08; Found:C, 69.56; H, 5.24; N, 10.08%. [α]_D^{20°} = +297.9° (C=1.21; CHCl₃).

EXAMPLE 9

Cis-2,3,6,7,12,12a-hexahydro-2-[2-(2-pyridyl)-ethyl]-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 2-(2pyridyl)ethylamine and intermediate 1 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p.:218°-222° C.

Analysis for C₂₈H₂₄N₄O₄: Calculated:C, 69.99; H, 5.03; N, 11.66; Found:C, 69.92; H, 5.16; N, 11.48%.

EXAMPLE 10

Cis-2,3,6,7,12,12a-hexahydro-2-(2-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 2-pyridylmethylamine and intermediate 1 gave, after recrystallisation from DMF/water, the title compound as cream crystals m.p.:285°-286° C.

Analysis for $C_{27}H_{22}N_4O_4$ (0.4 H₂O): Calculated: C, 68.46; H, 4.85; N, 11.83; Found: C, 68.58; H, 4.88; N, 11.90%.

EXAMPLE 11

Cis-2,3,6,7,12,12a-hexahydro-2-(3-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 3-pyridylmethylamine and intermediate 1 gave, after recrystallisation from CH₂Cl₂/MeOH, the title compound as cream crystals m.p.:292°-293° C.

Analysis: $C_{27}H_{22}N_4O_4$: Calculated: C, 69.52; H, 4.75; N, 12.01; Found: C, 69.27; H, 4.74; N, 11.37%.

EXAMPLE 12

Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 4-pyridylmethylamine and intermediate 1 gave, after recrystallisation from MeOH, the title compound as pale yellow crystals m.p.:273°-274° C.

Analysis for $C_{27}H_{22}N_4O_4$ (1.8 H₂O): Calculated: C, 65.00; H, 5.17; N, 11.23; Found: C, 65.11; H, 4.85; N, 11.07%.

EXAMPLE 13

Cis-2,3,6,7,12,12a-hexahydro-2-ethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from ethylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:272°-274° C.

Analysis for $C_{22}H_{21}N_3O_4$: Calculated: C, 68.47; H, 5.25; N, 10.42; Found: C, 68.52; H, 5.35; N, 10.53%.

EXAMPLE 14

Cis-2,3,6,7,12,12a-hexahydro-2-(2,2,2-trifluoroethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 2,2,2-trifluoroethylamine and intermediate 1 gave, after recrystallisation from EtOH, the title compound as white crystals m.p.:303° C.

Analysis for $C_{23}H_{18}F_3N_3O_4$: Calculated: C, 60.40; H, 3.97; N, 9.19; Found: C, 60.43; H, 4.15; N, 9.16%.

EXAMPLE 15

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-2-propyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from propylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals

m.p.:270°-271° C.

Analysis for $C_{24}H_{23}N_3O_4$: Calculated: C, 69.05; H, 5.55; N, 10.07; Found: C, 69.22; H, 5.50; N, 9.80%.

EXAMPLE 16

Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from isopropylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:248°-250° C.

Analysis for $C_{24}H_{23}N_3O_4$: Calculated: C, 69.05; H, 5.55; N, 10.07; Found: C, 68.86; H, 5.66; N, 10.21%.

EXAMPLE 17

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:290°-292° C.

Analysis for $C_{24}H_{21}N_3O_4$: Calculated: C, 69.39; H, 5.10; N, 10.11; Found: C, 69.11; H, 5.20; N, 9.94%.

EXAMPLE 18

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 1 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p.:241°-243° C.

Analysis for $C_{25}H_{25}N_3O_4$: Calculated: C, 69.59; H, 5.84; N, 9.74; Found: C, 69.77; H, 5.82; N, 9.81%.

EXAMPLE 19

Trans-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 2 gave, after recrystallisation from toluene, the title compound as white crystals m.p.:243° C.

Analysis for $C_{25}H_{25}N_3O_4$: Calculated: C, 69.59; H, 5.84; N, 9.74; Found: C, 69.80; H, 5.78; N, 9.52%.

EXAMPLE 20

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 1 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:217°-218° C.

Analysis for $C_{25}H_{23}N_3O_4$: Calculated: C, 69.92; H, 5.40; N, 9.78; Found: C, 70.02; H, 5.47; N, 9.84%.

EXAMPLE 21

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 1 gave, after recrystallisation from acetone, the title compound as white crystals m.p.:270° C.

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Analysis for $C_{26}H_{25}N_3O_4$: Calculated: C, 70.41; H, 5.68; N, 9.47; Found: C, 70.58; H, 5.63; N, 9.38%.

EXAMPLE 22

Cis-2,3,6,7,12,12a-hexahydro-2-cyclohexyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclohexylamine and intermediate 1 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p.: 268°-269° C.

Analysis for $C_{27}H_{27}N_3O_4$: Calculated: C, 70.88; H, 5.95; N, 9.18; Found: C, 70.82; H, 5.89; N, 9.21%.

EXAMPLE 23

Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from benzylamine and intermediate 1 gave, after recrystallisation from dichloromethane/hexane, the title compound as white crystals m.p.: 285°-287° C.

Analysis for $C_{28}H_{29}N_3O_4(1H_2O)$: Calculated: C, 69.55; H, 5.21; N, 8.69; Found: C, 69.30; H, 5.06; N, 8.48%.

EXAMPLE 24

Cis-2,3,6,7,12,12a-hexahydro-2-(4-fluorobenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 4-fluorobenzylamine and intermediate 1 gave, after recrystallisation from acetone, the title compound as white crystals m.p.: 281°-283° C.

Analysis for $C_{28}H_{27}FN_3O_4$: Calculated: C, 69.56; H, 4.59; F, 3.93; N, 8.69; Found: C, 69.54; H, 4.58; F, 3.82; N, 8.63%.

EXAMPLE 25

Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 3 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p.: 257°-263° C.

Analysis for $C_{22}H_{21}N_3O_3$: Calculated: C, 70.38; H, 5.64; N, 11.19; Found: C, 70.11; H, 5.55; N, 11.15%.

EXAMPLE 26

Trans-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 4 gave, after recrystallisation from diisopropyl ether, the title compound as white crystals m.p.: 225°-228° C.

Analysis for $C_{22}H_{21}N_3O_3$: Calculated: C, 70.38; H, 5.64; N, 11.19; Found: C, 70.34; H, 5.77; N, 11.19%.

EXAMPLE 27

Cis-2,3,6,7,12,12a-hexahydro-2-ethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from ethylamine and intermediate 3 gave, after recrystallisation from methanol, the title compound as white crystals

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m.p.: 245°-255° C.

Analysis for $C_{23}H_{23}N_3O_3$: Calculated: C, 70.93; H, 5.95; N, 10.79; Found: C, 70.74; H, 6.06; N, 10.87%.

EXAMPLE 28

Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 2,2,2-trifluoroethylamine and intermediate 3 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.: 232° C.

Analysis for $C_{23}H_{20}F_3N_3O_3$: Calculated: C, 62.30; H, 4.55; N, 9.48; Found: C, 62.08; H, 4.66; N, 9.54%.

EXAMPLE 29

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 3 gave, after recrystallisation from methanol, the title compound as white crystals m.p.: 157° C.

Analysis for $C_{25}H_{27}N_3O_3(0.5 H_2O)$: Calculated: C, 70.40; H, 6.62; N, 9.85; Found: C, 70.25; H, 6.60; N, 9.83%.

EXAMPLE 30

Trans-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 4 gave, after recrystallisation from methanol, the title compound as white crystals m.p.: 212°-214° C.

Analysis for $C_{25}H_{27}N_3O_3$: Calculated: C, 71.92; H, 6.52; N, 10.06; Found: C, 71.81; H, 6.55; N, 10.03%.

EXAMPLE 31

Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 3 gave, after recrystallisation from methanol, the title compound as white crystals m.p.: 180°-185° C.

Analysis for $C_{25}H_{25}N_3O_3(0.5 H_2O)$: Calculated: C, 70.74; H, 6.17; N, 9.90; Found: C, 70.91; H, 6.16; N, 9.80%.

EXAMPLE 32

Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from benzylamine and intermediate 3 gave, after recrystallisation from acetone, the title compound as white crystals m.p.: 275°-279° C.

Analysis for $C_{26}H_{25}N_3O_3$: Calculated: C, 74.48; H, 5.58; N, 9.31; Found: C, 74.53; H, 5.60; N, 9.20%.

EXAMPLE 33

Cis-2,3,6,7,12,12a-hexahydro-6-(3-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 5 gave, after recrystallisation from methanol, the title compound as white crystals

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m.p.:267°-269° C.

Analysis for $C_{22}H_{21}N_3O_3$: Calculated: C,70.38;H,5.64;N,11.19; Found: C,70.32;H,5.59;N,11.25%.

EXAMPLE 34

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 6 gave, after recrystallisation from methanol, the title compound as white crystals
m.p.:247°-248° C.

Analysis for $C_{22}H_{23}N_3O_3$: Calculated: C,70.93;H,5.95;N,10.79; Found: C,71.23;H,5.95;N,10.63%.

EXAMPLE 35

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethoxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 6 gave, after recrystallisation from 2-propanol, the title compound as white crystals
m.p.:160°-162° C.

Analysis for $C_{26}H_{27}N_3O_3$: Calculated: C,72.71;H,6.34;N,9.78; Found: C,72.28;H,6.39;N,9.71%.

EXAMPLE 36

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 8 gave, after recrystallisation from methanol, the title compound as white crystals
m.p.:292°-294° C.

Analysis for $C_{23}H_{21}N_3O_3$: Calculated: C,71.30;H,5.46;N,10.85; Found: C,71.15;H,5.56;N,10.84%.

EXAMPLE 37

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 8 gave, after recrystallisation from methanol, the title compound as white crystals
m.p.:165°-166° C.

Analysis for $C_{26}H_{25}N_3O_3$: Calculated: C,73.05;H,5.89;N,9.83; Found: C,73.08;H,5.97;N,9.87%.

EXAMPLE 38

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-ethylenedioxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 10 gave, after recrystallisation from acetone, the title compound as white crystals
m.p.:303°-305° C.

Analysis for $C_{23}H_{21}N_3O_4$: Calculated: C,68.47;H,5.25;N,10.42; Found: C,68.35;H,5.31;N,10.27%.

EXAMPLE 39

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-ethylenedioxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 10 gave, after recrystalli-

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sation from dichloromethane/ether, the title compound as white crystals m.p.:288°-290° C.

Analysis for $C_{26}H_{25}N_3O_4$: Calculated: C,70.41;H,5.68;N,9.47; Found: C,70.15;H,5.62;N,9.30%.

EXAMPLE 40

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(2-chlorophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 12 gave, after recrystallisation from methanol/water, the title compound as white crystals
m.p.:146° C.

Analysis for $C_{24}H_{24}ClN_3O_2(0.75 H_2O)$: Calculated: C,66.20;H,5.90;N,9.65; Found: C,66.15;H,5.95;N,9.69%.

EXAMPLE 41

Cis-2,3,6,7,12,12a-hexahydro-6-(4-chlorophenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 13 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:274° C.

Analysis for $C_{21}H_{19}ClN_3O_2(0.25 H_2O)$: Calculated: C,65.63;H,4.85;N,10.93; Found: C,65.39;H,4.84;N,10.85%.

EXAMPLE 42

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-chlorophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 13 gave, after recrystallisation from ethanol/water, the title compound as white crystals
m.p.:164°-166° C.

Analysis for $C_{24}H_{24}ClN_3O_2$: Calculated: C,68.32;H,5.73;Cl, 8.40;N,9.96; Found: C,68.48;H,5.64; Cl, 8.37;N,9.99%.

EXAMPLE 43

Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-dichlorophenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 15 gave, after recrystallisation from ethanol/DMF, the title compound as white crystals
m.p.:>260° C.

Analysis for $C_{21}H_{17}Cl_2N_3O_2(0.5 H_2O)$: Calculated: C,59.39;H,4.29;N,9.93; Found: C,59.32;H,4.16;N,9.99%.

EXAMPLE 44

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-phenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and cis-methyl 1,2,3,4-tetrahydro-1phenyl-9H-pyrido[3,4-b]indole-3-carboxylate¹ gave, after recrystallisation from methanol/water, the title compound as white crystals m.p.: 243°-245° C.

Analysis for $C_{24}H_{25}N_3O_2$: Calculated: C,74.39;H,6.50;N,10.84; Found: C,74.54;H,6.51;N,10.86%.

1. D. Soerens et al., J. Org. Chem. 44, 535-545 (1979).

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EXAMPLE 45

Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-phenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from benzylamine and cis-methyl-1,2,3,4-tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate gave, after recrystallisation from methanol, the title compound as white crystals m.p.:193-195° C.

Analysis for $C_{27}H_{23}N_3O_2$: Calculated:C,76.94;H,5.50;N,9.97; Found:C,77.23;H,5.54;N,9.97%.

EXAMPLE 46

Trans-2,3,6,7,12,12a-hexahydro-2-benzyl-6-phenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from benzylamine and cis-methyl-1,2,3,4-tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate gave, after recrystallisation from methanol, the title compound as white crystals m.p.: 284° C.

Analysis for $C_{27}H_{23}N_3O_2$: Calculated:C,76.94;H,5.50;N,9.97; Found:C,76.88;H,5.45;N,9.89%.

EXAMPLE 47

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(1,2,3,4-tetrahydro-6-naphthyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 17 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:>260° C.

Analysis for $C_{25}H_{23}N_3O_2$: Calculated:C,75.16;H,6.31;N,10.52; Found:C,74.93;H,6.43;N,10.63%.

EXAMPLE 48

Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(1,2,3,4-tetrahydro-6-naphthyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from isopropylamine and intermediate 17 gave, after recrystallisation from the title compound as off-white crystals m.p.:244°-246° C.

Analysis for $C_{27}H_{29}N_3O_2$ (0.25 H₂O): Calculated:C,75.06;H,6.88;N,9.73; Found:C,75.00;H,6.83;N,9.69%.

EXAMPLE 49

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(1,2,3,4-tetrahydro-6-naphthyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 17 gave, after recrystallisation from ethanol/pentane, the title compound as white crystals m.p.:125° C.

Analysis for $C_{28}H_{29}N_3O_2$ (0.25 H₂O): Calculated:C,75.73;H,6.70;N,9.46; Found:C,75.45;H,6.86;N,9.14%.

EXAMPLE 50

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(2-naphthyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 18 gave, after recrystallisation from

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dichloromethane/methanol, the title compound as white crystals m.p.:>260° C.

Analysis for $C_{25}H_{21}N_3O_2$ (0.25 H₂O): Calculated:C,75.08;H,5.42;N,10.51; Found:C,75.35;H,5.42;N,10.49%.

EXAMPLE 51

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(2-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 20 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:226° C.

Analysis for $C_{22}H_{23}N_3O_2S$: Calculated:C,67.15;H,5.89;N,10.68; Found:C,67.39;H,5.88;N,10.77%.

EXAMPLE 52

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 24 gave, after recrystallisation from ethanol, the title compound as a cream powder m.p.:258° C.

Analysis for $C_{19}H_{16}BrN_3O_2S$: Calculated:C,53.03;H,3.75;N,9.76; Found:C,53.01;H,3.78;N,9.69%.

EXAMPLE 53

Cis-2,3,6,7,12,12a-hexahydro-6-(4-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 26 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:292° C.

Analysis for $C_{19}H_{16}BrN_3O_2S$ (0.25 H₂O): Calculated:C,52.48;H,3.82;N,9.66; Found:C,52.46;H,3.81;N,9.60%.

EXAMPLE 54

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 24 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:190° C.

Analysis for $C_{22}H_{20}BrN_3O_2S$: Calculated:C,56.18;H,4.29;N,8.93; Found:C,55.92;H,4.28;N,8.74%.

EXAMPLE 55

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-cyclopentyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 24 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:252° C.

Analysis for $C_{23}H_{22}BrN_3O_2S$: Calculated:C,57.03;H,4.58;N,8.67; Found:C,56.87;H,4.66;N,8.68%.

EXAMPLE 56

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(5-methyl-2-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and the cis isomer of intermediate 66 gave, after

recrystallisation from ethanol, the title compound as white crystals m.p.:282° C.

Analysis for $C_{20}H_{19}N_3O_2S$ (0.25 H_2O): Calculated:C, 64.93;H,5.31;N,11.36; Found:C,64.84;H,5.28;N,10.81%.

EXAMPLE 57

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 22 gave, after recrystallisation from acetone, the title compound as white crystals m.p.:290°-295° C.

Analysis for $C_{19}H_{17}N_3O_2S$: Calculated:C,64.94;H,4.88;N,11.96; Found:C,64.81;H,4.95;N,11.68%.

EXAMPLE 58

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 22 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:236°-239° C.

Analysis for $C_{22}H_{23}N_3O_2S$: Calculated:C,67.15;H,5.89;N,10.68;S,8.15; Found:C,67.42;H,5.76;N,10.57;S,8.01%.

EXAMPLE 59

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-furyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and the cis isomer of intermediate 28 gave, after recrystallisation from ether, the title compound as a white solid m.p.:250° C.

Analysis for $C_{19}H_{17}N_3O_3$ (0.5 H_2O): Calculated:C, 66.27;H,5.27;N,12.20; Found:C,66.33;H,5.48;N,12.02%.

EXAMPLE 60

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(5-methyl-2-furyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 29 gave, after recrystallisation from ethanol, the title compound as a cream powder m.p.:303° C.

Analysis for $C_{20}H_{19}N_3O_3$ (0.25 H_2O): Calculated:C, 67.88;H,5.55;N,11.87; Found:C,67.90;H,5.50;N,11.98%.

EXAMPLE 61

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 31 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:>260° C.

Analysis for $C_{22}H_{21}N_3O_2$ (0.25 H_2O): Calculated:C, 72.61;H,5.95;N,11.55; Found:C,72.73;H,5.96;N,11.59%.

EXAMPLE 62

Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from isopropylamine and intermediate 31 gave, after recrystallisation from the title compound as white crystals m.p.:170° C.

Analysis for $C_{24}H_{25}N_3O_2$ (0.5 H_2O): Calculated:C, 72.70;H,6.61;N,10.60; Found:C,73.06;H,6.43;N,9.66%.

EXAMPLE 63

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 31 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:194° C.

Analysis for $C_{25}H_{27}N_3O_2$ (0.5 H_2O): Calculated:C, 73.15;H,6.87;N,10.24; Found:C,73.01;H,6.84;N,10.26%.

EXAMPLE 64

Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 31 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p.:194° C.

Analysis for $C_{25}H_{25}N_3O_2$ (1.1 H_2O): Calculated:C, 71.61;H,6.54;N,10.02; Found:C,71.42;H,6.07;N,9.95%.

EXAMPLE 65

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 33 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:>260° C.

Analysis for $C_{22}H_{21}N_3O_2$: Calculated:C,73.52;H,5.89;N,11.69; Found:C,73.60;H,5.97;N,11.66%.

EXAMPLE 66

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-trifluoromethylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 35 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p.:155° C.

Analysis for $C_{25}H_{24}F_3N_3O_2$ (0.5 H_2O): Calculated:C, 64.65;H,5.43;N,9.05; Found:C,64.78;H,5.40;N,9.01%.

EXAMPLE 67

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-trifluoromethoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and the cis isomer of intermediate 65 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:174°-180° C.

Analysis for $C_{22}H_{18}F_3N_3O_3$ (0.5 H_2O): Calculated:C, 60.27;H,4.37;N,9.58; Found:C,60.24;H,4.28;N,9.50%.

EXAMPLE 68

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-hydroxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 39 gave, after recrystallisation from

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methanol, the title compound as yellow crystals m.p.:179°-180° C.

Analysis for $C_{22}H_{19}N_3O_3$ (1.25 H_2O): Calculated: C, 65.70; H, 5.64; N, 10.94; Found: C, 65.46; H, 5.45; N, 10.92%.

EXAMPLE 69

Cis-2,3,6,7,12,12a-hexahydro-6-(3-hydroxy-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 40 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:320° C.

Analysis for $C_{22}H_{21}N_3O_4$ (0.25 H_2O): Calculated: C, 66.74; H, 5.47; N, 10.61; Found: C, 66.72; H, 5.46; N, 10.53%.

EXAMPLE 70

Cis-2,3,6,7,12,12a-hexahydro-6-(4-hydroxy-3-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 41 gave, after recrystallisation from dichloromethane/ethanol, the title compound as yellow crystals m.p.:264°-265° C.

Analysis for $C_{22}H_{21}N_3O_4$: Calculated: C, 67.51; H, 5.41; N, 10.74; Found: C, 67.05; H, 5.41; N, 10.62%.

EXAMPLE 71

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-cyanophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 37 gave, after recrystallisation from methanol/water, the title compound as white crystals m.p.:246° C.

Analysis for $C_{25}H_{24}N_4O_2$ (1 H_2O): Calculated: C, 69.75; H, 6.09; N, 13.01; Found: C, 69.50; H, 5.96; N, 12.86%.

EXAMPLE 72

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-isopropyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from isopropylamine and the cis isomer of intermediate 42 gave, after recrystallisation from n-pentane, the title compound as white crystals m.p.:130° C.

Analysis for $C_{25}H_{27}N_3O_2$ (0.5 H_2O): Calculated: C, 73.15; H, 6.87; N, 10.24; Found: C, 73.39; H, 7.08; N, 9.81%.

EXAMPLE 73

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and the cis isomer of intermediate 42 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:160° C.

Analysis for $C_{26}H_{27}N_3O_2$: Calculated: C, 75.52; H, 6.58; N, 10.16; Found: C, 75.54; H, 6.62; N, 10.08%.

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EXAMPLE 74

Cis-2,3,6,7,12,12a-hexahydro-6-(4-isopropylphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 43 gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:244° C.

Analysis for $C_{24}H_{25}N_3O_2$: Calculated: C, 74.39; H, 6.50; N, 10.84; Found: C, 74.27; H, 6.53; N, 11.05%.

EXAMPLE 75

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-nitrophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 45 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:182° C.

Analysis for $C_{24}H_{24}N_4O_4$ (0.25 H_2O): Calculated: C, 65.97; H, 5.65; N, 12.82; Found: C, 65.92; H, 5.62; N, 12.96%.

EXAMPLE 76

Cis-2,3,6,7,12,12a-hexahydro-6-(4-dimethylaminophenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and the cis isomer of intermediate 47 gave after recrystallisation from methanol, the title compound as white crystals m.p.:266° C.

Analysis for $C_{23}H_{24}N_4O_2$: Calculated: C, 71.11; H, 6.23; N, 14.42; Found: C, 71.19; H, 6.24; N, 14.34%.

EXAMPLE 77

Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-pyridyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 48 gave after recrystallisation from chloroform, the title compound as white crystals m.p.:312° C.

Analysis for $C_{20}H_{18}N_4O_2$: Calculated: C, 69.35; H, 5.24; N, 16.17; Found: C, 69.08; H, 5.20; N, 16.19%.

EXAMPLE 78

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

a) To a stirred solution of intermediate 54 (0.5 g) and $NaHCO_3$ (0.14 g) in anhydrous $CHCl_3$ (20 mL) was added dropwise chloroacetyl chloride (0.27 mL) at 0° C. The resulting mixture was stirred for 1 hour at the same temperature and diluted with $CHCl_3$ (20 mL). Water (10 mL) was then added dropwise with stirring to the mixture, followed by a saturated solution of $NaHCO_3$. The organic layer was washed with water until neutrality and dried over Na_2SO_4 . After evaporation of the solvent under reduced pressure, (6R, 12aR)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate was obtained as an oil which was crystallised from ether to give a solid (0.38 g, m.p.:233° C.) which was used without further purification in the next step.

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b) To a stirred suspension of the chloroacetyl intermediate (0.37 g) in MeOH (20 mL) was added at room temperature a solution of methylamine (33% in EtOH) (0.4 mL) and the resulting mixture was heated at 50° C. under N₂ for 16 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (50 mL). After washing with water (3×20 mL), drying over Na₂SO₄ and evaporating to dryness, the residue was purified by flash chromatography eluting with CH₂Cl₂/MeOH (99/1) and recrystallised from 2-propanol to give the title compound as white crystals (0.22 g) m.p.:302°–303° C.

Analysis for C₂₂H₁₉N₃O₄: Calculated:C,67.86;H,4.92;N,10.79; Found:C,67.77;H,4.92;N,10.74%.

[α]_D²⁰ = +71.0° (C=1.00; CHCl₃).

The following compounds were obtained in a similar manner:

EXAMPLE 79

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from isopropylamine and intermediate 54 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:290°–293° C.

Analysis for C₂₄H₂₃N₃O₄: Calculated:C,69.05;H,5.55;N,10.07; Found:C,69.06;H,5.49;N,10.12%.

[α]_D²⁰ = +52.6° (C=1.14; CHCl₃).

EXAMPLE 80

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 54 gave, after recrystallisation from toluene/hexane, the title compound as white crystals m.p.:209°–210° C.

Analysis for C₂₅H₂₅N₃O₄: Calculated:C,69.59;H,5.84;N,9.74; Found:C,69.70;H,5.93;N,9.74%.

[α]_D²⁰ = +50.2° (C=0.53; CHCl₃).

EXAMPLE 81

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isobutyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 54 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:227°–228° C.

Analysis for C₂₅H₂₅N₃O₄: Calculated:C,69.59;H,5.84;N,9.74; Found:C,69.52;H,5.87;N,9.74%.

[α]_D²⁰ = +45° (C=1.04; CHCl₃).

EXAMPLE 82

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 54 gave, after recrystallisation from ether, the title compound as white crystals m.p.:237°–239° C.

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Analysis for C₂₆H₂₅N₃O₄: Calculated:C,70.41;H,5.68;N,9.47; Found:C,70.13;H,5.67;N,9.42%.

[α]_D²⁰ = +36.6° (C=0.98; CHCl₃).

EXAMPLE 83

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-2-cyclohexylmethyl-pyrazino[2',1':6,1]pyrido[3,4b]indole-1,4-dione

The same two step procedure but starting from cyclopentylamine and the cis isomer of intermediate 56 gave, after recrystallisation from 2-propanol the title compound as white crystals m.p.:209° C.

Analysis for C₂₈H₂₉N₃O₄: Calculated:C,71.32;H,6.20;N,8.91; Found:C,71.30;H,6.29;N,8.74%.

[α]_D²⁰ = +40.0° (C=0.99; CHCl₃).

EXAMPLE 84

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 57 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:204°–205° C.

Analysis for C₂₅H₂₅N₃O₃ (0.5 H₂O): Calculated:C,70.74;H,6.17;N,9.90; Found:C,70.98;H,6.09;N,9.92%.

[α]_D²⁰ = +54.1° (C=1.03; CHCl₃).

EXAMPLE 85

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from butylamine and intermediate 57 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p.:183°–184° C.

Analysis for C₂₅H₂₇N₃O₃ (0.5 H₂O): Calculated:C,70.40;H,6.62;N,9.85; Found:C,70.55;H,6.64;N,9.92%.

[α]_D²⁰ = +45.4° (C=1.04; CHCl₃).

EXAMPLE 86

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 57 gave, after recrystallisation from ether, the title compound as white crystals m.p.:210°–211° C.

Analysis for C₂₆H₂₇N₃O₃: Calculated:C,72.71;H,6.34;N,9.78; Found:C,72.53;H,6.39;N,9.53%.

[α]_D²⁰ = +29.8° (C=1.07; CHCl₃).

EXAMPLE 87

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 59 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:218°–219° C.

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Analysis for $C_{25}H_{24}ClN_3O_3$ (0.25 H_2O): Calculated: C, 66.08; H, 5.43; N, 9.25; Cl, 7.80; Found: C, 66.11; H, 5.33; N, 9.03; Cl, 7.74%.

$[\alpha]_D^{20} = +49.4^\circ$ (C=1.03; $CHCl_3$).

EXAMPLE 88

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3-chloro-4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopentylamine and intermediate 59 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:260°-262° C.

Analysis for $C_{26}H_{26}ClN_3O_3$: Calculated: C, 67.31; H, 5.65; Cl, 7.64; N, 9.06; Found: C, 66.98; H, 5.67; Cl, 8.06; N, 9.04%.

$[\alpha]_D^{20} = +27.60^\circ$ (C=1.05; $CHCl_3$).

EXAMPLE 89

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 59 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:283°-284° C.

Analysis for $C_{22}H_{20}ClN_3O_3$: Calculated: C, 64.47; H, 4.92; Cl, 8.65; N, 10.25; Found: C, 64.49; H, 4.92; Cl, 8.33; N, 10.02%.

$[\alpha]_D^{20} = +61.3^\circ$ (C=1.00; $CHCl_3$).

EXAMPLE 90

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3-chloro-4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from isopropylamine and intermediate 59 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:302°-304° C.

Analysis for $C_{24}H_{24}ClN_3O_3$: Calculated: C, 65.83; H, 5.52; N, 9.60; Found: C, 65.83; H, 5.57; N, 9.73%.

$[\alpha]_D^{20} = +39.8^\circ$ (C=0.95; $CHCl_3$).

EXAMPLE 91

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 61 gave, after recrystallisation from dichloromethane/methanol, the title compound as white crystals m.p.:288°-291° C.

Analysis for $C_{23}H_{21}N_3O_3$: Calculated: C, 71.30; H, 5.46; N, 10.85; Found: C, 71.27; H, 5.49; N, 10.96%.

$[\alpha]_D^{20} = +65.6^\circ$ (C=0.4; $CHCl_3$).

EXAMPLE 92

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methylcyclopropyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylcyclopropylamine and intermediate 61 gave, after recrystal-

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lisation from methanol, the title compound as white crystals m.p.:242°-244° C.

Analysis for $C_{26}H_{25}N_3O_3$: Calculated: C, 73.05; H, 5.89; N, 9.83; Found: C, 72.90; H, 5.93; N, 9.98%.

$[\alpha]_D^{20} = +55.4^\circ$ (C=0.99; $CHCl_3$).

EXAMPLE 93

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indanyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 63 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:262° C.

Analysis for $C_{24}H_{23}N_3O_2$: Calculated: C, 74.78; H, 6.01; N, 10.90; Found: C, 74.65; H, 5.90; N, 10.67%.

$[\alpha]_D^{20} = +68.6^\circ$ (C=0.98; $CHCl_3$).

EXAMPLE 94

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indanyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from cyclopropylmethylamine and intermediate 63 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:176° C.

Analysis for $C_{27}H_{27}N_3O_2$ (0.25 H_2O): Calculated: C, 75.41; H, 6.45; N, 9.77; Found: C, 75.25; H, 6.51; N, 9.75%.

$[\alpha]_D^{20} = +57.9^\circ$ (C=1.00; $CHCl_3$).

EXAMPLE 95

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1-b]pyrido[3,4-b]indole-1,4-dione

To a stirred suspension of Intermediate 73 (12.5 g) in MeOH (400 ml) was added at room temperature a solution of methylamine (33% in EtOH) (13.7 ml) and the resulting mixture was heated at 50° C. under N_2 for 14 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (1l). After washing with water (3x500 ml), drying over Na_2SO_4 and evaporating to dryness, the white solid obtained was recrystallised from 2-propanol to give the title compound as white needles (7.5 g).

mp:298°-300° C.

$[\alpha]_D^{20} = +71.3^\circ$ (c=0.55, $CHCl_3$).

Elemental analysis ($C_{22}H_{19}N_3O_4$) calculated: C, 67.86; H, 4.92; N, 10.79; found: C, 67.79; H, 4.95; N, 10.61%.

EXAMPLE 96

Cis-2,3,6,7,12,12a-hexahydro-2,10-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure as used to prepare Example 1, but starting from methylamine and the cis isomer of Intermediate 74, gave after recrystallisation from ethanol, the title compound as white crystals m.p.:275° C.

Analysis for $C_{23}H_{21}N_3O_4$ (0.4 H_2O): Calculated: C, 67.27; H, 5.35; N, 10.23; Found: C, 67.36; H, 5.21; N, 10.31%.

EXAMPLE 97

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-dimethoxybenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure as used to prepare Example 78, but starting from veratrylamine and intermediate 54

gave, after recrystallisation from methanol, the title compound as white crystals m.p.:224°–226° C.

Analysis for $C_{30}H_{27}N_3O_6$: Calculated: C,68.56;H,5.18;N,8.00; Found: C,68.80;H,5.11;N,8.06%.

$[\alpha]_D^{20} = +43.9^\circ$ (c=1.02; $CHCl_3$).

EXAMPLE 98

Cis-2,3,6,7,12,12a-hexahydro-6-(4-aminophenyl)-2-butyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

To a solution of Example 75 (1.5 g) in methanol (100 mL) was added $SnCl_2 \cdot H_2O$ (3.06) and the resulting mixture was heated at reflux for 8 hours. The mixture was cooled to ambient temperature, poured into ice and was adjusted to pH5 with 1N NaOH. The methanol was evaporated off and the residue was basified to pH11 with 1N NaOH and extracted with EtOAc (2x150 mL). After drying over Na_2SO_4 and evaporation of EtOAc, the resulting yellow powder was purified by radial chromatography eluting with CH_2Cl_2 to give the title compound as a white powder (550 mg) m.p.:192° C.

Analysis for $C_{24}H_{26}N_4O_2$ (1.3 H_2O): Calculated: C,67.68;H,6.77;N,13.15; Found: C,67.74;H,6.68;N,13.02%.

EXAMPLE 99

Cis-2,3,6,7,12,12a-hexahydro-6-(4-acetamidophenyl)-2-butyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

To a solution of Example 98 (0.2 g) in THF (15 mL) was added triethylamine (76 μ L) and acetyl chloride (39 μ L) and the resulting solution was stirred at room temperature for 2 hours. After evaporation of THF, the resulting residue was taken up in CH_2Cl_2 (100 mL), washed with water (2x50 mL) and dried over Na_2SO_4 . After evaporation of CH_2Cl_2 , the resulting solid was recrystallised from MeOH/ H_2O to give the title compound as a cream powder (120 mg) m.p.: 246° C.

Analysis for $C_{26}H_{28}N_4O_3$: Calculated: C,70.25;H,6.35;N,12.60; Found: C,69.85;H,6.38;N,12.56%.

EXAMPLE 100

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylsulfonamidophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

To a solution of Example 98 (0.2 g) in THF (5 mL) was added triethylamine (228 μ L) and methanesulfonyl chloride (126 μ L) and the solution was heated at reflux for 6 hours. After evaporation of THF, the residue was taken up in CH_2Cl_2 , washed with water and dried over Na_2SO_4 . After evaporation of CH_2Cl_2 , the residue was purified by radial chromatography eluting with CH_2Cl_2 /MeOH (95/5) to give the title compound as a brown powder (30 mg) m.p.:188° C.

Analysis for $C_{25}H_{28}N_4O_4S$ (0.75 H_2O): Calculated: C,60.77;H,6.02;N,11.34; Found: C,60.61;H,6.02;N,10.82%.

EXAMPLE 101

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from ammonia and intermediate 54 gave, after recrystallisation from methanol, the title compound as white crystals

m.p.:285°–290° C.

Analysis for $C_{21}H_{17}N_3O_4$: Calculated: C,67.19;H,4.56;N,11.19; Found: C,67.30;H,4.66;N,11.11%.

$[\alpha]_D^{20} = +88^\circ$ (c=0.48; pyridine).

EXAMPLE 102

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-2-(2-propynyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from propargylamine and intermediate 54 gave, after recrystallisation from acetone, the title compound as white crystals m.p.:271° C.

Analysis for $C_{24}H_{19}N_3O_4$: Calculated: C,69.72;H,4.63;N,10.16; Found: C,69.95;H,4.66;N,10.06%.

$[\alpha]_D^{20} = +51.7^\circ$ (c=0.49; $CHCl_3$).

EXAMPLE 103

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-methylenedioxyphenyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from piperonylamine and intermediate 54 gave, after recrystallisation from methanol, the title compound as white

crystals m.p.:204°–206° C. Analysis for $C_{29}H_{23}N_3O_6$: Calculated: C,68.36;H,4.55;N,8.25; Found: C,68.25;H,4.49;N,8.41.

$[\alpha]_D^{20} = +43^\circ$ (c=1.01; $CHCl_3$).

EXAMPLE 104

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-dimethoxyphenethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 3,4-dimethoxyphenethylamine and intermediate 54 gave, after recrystallisation from dichloromethane/ether, the title compound as white crystals m.p.:265°–266° C.

Analysis for $C_{31}H_{29}N_3O_6$: Calculated: C,69.00;H,5.42;N,7.79; Found: C,68.68;H,5.35;N,7.78%.

$[\alpha]_D^{20} = +38.3^\circ$ (c=1.12; $CHCl_3$).

EXAMPLE 105

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-furfuryl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from furfurylamine and intermediate 54 gave, after recrystallisation from methanol, the title compound as white crystals m.p. 219° C.

Analysis for $C_{26}H_{21}N_3O_5$: Calculated: C,68.56;H,4.65;N,9.23; Found: C,68.16;H,4.63;N,9.15%.

$[\alpha]_D^{20} = +58.1^\circ$ (c=1.2; $CHCl_3$).

EXAMPLE 106

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-2-(2-thienylmethyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from 2-thiophenemethylamine and intermediate 54 gave, after

recrystallisation from methanol/water, the title compound as white crystals m.p.:155°-157° C.

Analysis for $C_{26}H_{21}N_3O_4S$: Calculated:C,66.23;H,4.49;N,8.91;S,6.8; Found:C,66.13;H,4.54;N,9.12;S,6.78%.

$[\alpha]_D^{20} = +70.4^\circ$ (c=1.03; $CHCl_3$).

EXAMPLE 107

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and intermediate 57 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:285°-288° C.

Analysis for $C_{22}H_{21}N_3O_3$: Calculated:C,70.38;H,5.64;N,11.19; Found:C,70.31;H,5.69;N,11.29%.

$[\alpha]_D^{20} = +59^\circ$ (c=1.19; $CHCl_3$).

EXAMPLE 108

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-ethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from ethylamine and intermediate 57 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:277° C.

Analysis for $C_{23}H_{23}N_3O_3$: Calculated:C,70.93;H,5.95;N,10.79; Found:C,70.90;H,5.96;N,10.54%.

$[\alpha]_D^{20} = +52^\circ$ (c=1.28; $CHCl_3$).

EXAMPLE 109

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(7-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazinyll)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from intermediate 75 and methylamine gave, after recrystallisation from ethanol, the title compound as white crystals m.p.:285°-288° C.

Analysis for $C_{24}H_{24}N_4O_3$ (0.5H₂O): Calculated:C,67.75;H,5.92;N,13.17; Found:C,68.02;H,6.00;N,13.18%.

$[\alpha]_D^{20} = +71.7^\circ$ (c=1, pyridine).

EXAMPLE 110

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-(N-benzylindolinyl))-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from intermediate 77 and methylamine gave, after recrystallisation from dichloromethane/methanol, the title compound as white crystals m.p.:223°-225° C.

Analysis for $C_{30}H_{28}N_4O_2$: Calculated:C,75.61;H,5.92;N,11.76; Found:C,75.2;H,5.78;N,11.67%.

$[\alpha]_D^{20} = +20.4^\circ$ (c=0.5, $CHCl_3$).

EXAMPLE 111

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-(5-indolinyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

A solution of Example 110 (1.05 g, 2.2 mmol) in methanol (100 mL) was hydrogenated in the presence of

10% Pd-C (100 mg) for 48 hours at room temperature. After removal of the catalyst, the solvent was evaporated in vacuo to leave a residue which was purified by flash chromatography eluting with dichloromethane/methanol:96/4. The solid obtained was recrystallised from dichloromethane/methanol to give the title compound (300 mg) as white crystals

m.p.:240° C.

Analysis for $C_{23}H_{22}N_4O_2$ (0.5H₂O): Calculated:C,69.86;H,5.86;N,14.17; Found:C,70.13;H,5.77;N,14.06%.

$[\alpha]_D^{20} = +55.9^\circ$ (C=1.18; pyridine).

EXAMPLE 112

Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from methylamine and the cis isomer of intermediate 42 gave, after recrystallisation from methanol, the title compound as white crystals m.p.:254° C.

Analysis for $C_{23}H_{23}N_3O_2$ (0.25 H₂O): Calculated:C,73.09;H,6.27;N,11.12; Found:C,73.03;H,6.18;N,11.36%.

EXAMPLE 113

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(4-carbomethoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two step procedure but starting from intermediate 78 (cis isomer) and methylamine gave, after recrystallisation from methanol, the title compound as white crystals m.p.:308°-312° C.

Analysis for $C_{23}H_{21}N_3O_4$: Calculated:C,68.47;H,5.25;N,10.42; Found:C,68.76;H,5.18;N,10.35%.

$[\alpha]_D^{20} = +97.7^\circ$ (c=1, pyridine).

EXAMPLE 114

(5aR,12R,14aR)-1,2,3,5a,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1',2':4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione

A solution of intermediate 80 (0.7 g, 1.2 mmol) in a mixture of methanol/THF (80/40 mL) was hydrogenated in the presence of 10% Pd-C (75 mg) for 48 hours at 40° C. After removal of the catalyst, the solvent was evaporated in vacuo to leave a residue, which was purified by flash chromatography eluting with dichloromethane/methanol:98/2. The white solid obtained was recrystallised from methanol to give the title compound (180 mg) as white crystals m.p.:284°-287° C.

Analysis for $C_{24}H_{21}N_3O_4$: Calculated:C,69.39;H,5.10;N,10.11; Found:C,69.47;H,5.11;N,9.97%.

$[\alpha]_D^{20} = +21.7^\circ$ (c=0.64, $CHCl_3$).

EXAMPLE 1.15

(5aR,12R,14aS)-1,2,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1',2':4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione

A solution of intermediate 81 (0.89, 1.37 mmol) in methanol (40 mL) was hydrogenated in the presence of 10% Pd-C (100 mg) for 5 h at 45° C. After removal of the catalyst the solvent was evaporated in vacuo to leave a residue,

which was purified by flash chromatography eluting with dichloromethane/methanol :98/2. The solid obtained was recrystallised from methanol to give the title compound (300 mg) as white crystals m.p.:302–304° C.

Analysis for $C_{24}H_{21}N_3O_4$: Calculated:C,69.39;H,5.10;N,10.11; Found:C,69.35;H,5.11;N,10.10%.

$[\alpha]_D^{20} +106.8^\circ$ (c=1.08, $CHCl_3$).

EXAMPLE 116

(3R,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

To a stirred solution of intermediate 82 (0.15 g, 0.34 mmol) in THF (15 mL) was added at room temperature a solution of methylamine (33% in EtOH) (0.32 mL) and the resulting solution was heated at reflux under N_2 for 24 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (25 mL). After washing with water (2x20 mL), drying over Na_2SO_4 and evaporating to dryness, the crude product was purified by flash chromatography eluting with dichloromethane/methanol:99/1. The white solid obtained was recrystallised from methanol to give the title compound as white crystals (80 mg)

m.p.:219°–220° C.

Analysis for $C_{23}H_{21}N_3O_4$: Calculated:C,68.47;H,5.25;N,10.42; Found:C,68.39;H,5.21;N,10.42%.

$[\alpha]_D^{20} +89.6^\circ$ (c=1; $CHCl_3$).

EXAMPLE 117

(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

To a stirred solution of intermediate 83 (0.3 g, 0.68 mmol) in THF (30 mL) was added at room temperature a solution of methylamine (33% in EtOH) (0.68 mL) and the resulting solution was treated at reflux under N_2 for 6 days. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). After washing with water (2,25 mL), drying over Na_2SO_4 and evaporating to dryness, the crude product was purified by flash chromatography eluting with dichloromethane/methanol :99/1. The oily residue obtained was crystallised from methanol to give the title compound as white crystals (40 mg)

m.p.:307°–309° C.

Analysis for $C_{23}H_{21}N_3O_4$: Calculated:C,68.47;H,5.25;N,10.42; Found:C,68.35;H,5.33;N,10.42%.

$[\alpha]_D^{20} +65.2^\circ$ (c=1.15; $CHCl_3$).

EXAMPLE 118

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-dihydroxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

A solution of intermediate 86 (0.75 g; 1.34 mmol) in a mixture of ethanol/THF (70/30 mL) was hydrogenated in the presence of 10% Pd-C (75 mg) for 24 h at room temperature. After removal of the catalyst, the solvent was evaporated in vacuo to leave a white solid which was recrystallised from methanol to give the title compound (0.35 g) as white crystals m.p.:224°–226° C.

Analysis for $C_{21}H_{19}N_3O_4$: Calculated:C,66.83;H,5.07;N,11.13; Found:C,66.58;H,5.01;N,11.04%.

$[\alpha]_D^{20} +58.4^\circ$ (c=1.04; pyridine).

EXAMPLE 119

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(5-(2-methylisindolinyl))pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

The same two steps procedure but starting from intermediate 87 and methylamine gave a crude oil which was purified by flash chromatography eluting with dichloromethane/methanol/triethylamine :92/8/0.1%. The solid obtained was recrystallized from isopropanol/propyl ether/water to give the title compound (20 mg) as off-white crystals m.p.:236° C.

Analysis for $C_{24}H_{24}N_4O_2$ (2.68 H_2O) Calculated:C,64.23;H,6.59;N,12.48; Found:C,64.21;H,6.43;N,12.02%.

$[\alpha]_D^{20} +61.1^\circ$ (c=0.5; CH_3OH).

EXAMPLE 120

Compounds of formula (I) have been included in pharmacy formulations and details of such formulations are given below.

TABLETS FOR ORAL ADMINISTRATION

A. Direct Compression

1.	mg/tablet
Active ingredient	50.0
Crospovidone USNF	8.0
Magnesium Stearate Ph Eur	1.0
Anhydrous Lactose	141.0

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets.

2.	mg/tablet
Active ingredient	50.0
Colloidal Silicon Dioxide	0.5
Crospovidone	8.0
Sodium Lauryl Sulphate	1.0
Magnesium Stearate Ph Eur	1.0
Microcrystalline Cellulose USNF	139.5

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets.

B. WET GRANULATION

1.	mg/tablet
Active ingredient	50.0
Polyvinyl pyrrolidone	150.0
Polyethylene glycol	50.0
Polysorbate 80	10.0
Magnesium Stearate Ph Eur	2.5
Croscarmellose Sodium	25.0
Colloidal Silicon Dioxide	2.5
Microcrystalline Cellulose USNF	210.0

The polyvinyl pyrrolidone, polyethylene glycol and polysorbate 80 were dissolved in water. The resultant solution was used to granulate the active ingredient. After drying the granules were screened, then extruded at elevated temperatures and pressures. The extrudate was milled and/or screened then was blended with the microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide

and magnesium stearate. The resultant mix was compressed into tablets.

2.	mg/tablet
Active ingredient	50.0
Polysorbate 80	3.0
Lactose Ph Eur	178.0
Starch BP	45.0
Pregelatinised Maize Starch BP	22.5
Magnesium Stearate BP	1.5

The active ingredient was sieved and blended with the lactose, starch and pregelatinised maize starch. The polysorbate 80 was dissolved in purified water. Suitable volumes of the polysorbate 80 solution were added and the powders were granulated. After drying, the granules were screened and blended with the magnesium stearate. The granules were then compressed into tablets.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to the other excipients.

FILM COATED TABLETS

The aforementioned tablet formulations were film coated.

Coating Suspension	% w/w
Opadry white†	13.2
Purified water Ph Eur	to 100.0*

*The water did not appear in the final product. The maximum theoretical weight of solids applied during coating was 20 mg/tablet.

†Opadry white is a proprietary material obtainable from Colorcon Limited, UK which contains hydroxypropyl methylcellulose, titanium dioxide and triacetin.

The tablets were film coated using the coating suspension in conventional film coating equipment.

1.	mg/capsule
Active ingredient	50.0
Lactose	148.5
Polyvinyl pyrrolidone	100.0
Magnesium Stearate	1.5

The active ingredient was sieved and blended with the excipients. The mix was filled into size No. 1 hard gelatin capsules using suitable equipment.

2.	mg/capsule
Active ingredient	50.0
Microcrystalline Cellulose	233.5
Sodium Lauryl Sulphate	3.0
Croscopovidone	12.0
Magnesium Stearate	1.5

The active ingredient was sieved and blended with the excipients. The mix was filled into size No. 1 hard gelatin capsules using suitable equipment.

Other doses may be prepared by altering the ratio of active ingredient to excipient, the fill weight and if necessary changing the capsule size.

3.	mg/capsule
Active ingredient Labmaf M1944CS	50.0 to 1.0 ml

The active ingredient was sieved and blended with the Labrafil. The suspension was filled into soft gelatin capsules using appropriate equipment.

EXAMPLE 121

Inhibitory effect on cGMP-PDE

cGMP-PDE activity of compounds of the present invention was measured using a one-step assay adapted from Wells et al. (Wells, J. N., Baird, C. E., Wu, Y. J. and Hardman, J. G., *Biochim. Biophys. Acta* 384, 430 (1975)). The reaction medium contained 50 mM Tris-HCl, pH 7.5, 5 mM Mg-acetate, 250 µg/ml 5'-Nucleotidase, 1 mM EGTA and 0.15 µM 8-[H³]-cGMP. The enzyme used was a human recombinant PDE V (ICOS, Seattle USA).

Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30%.

The IC₅₀ values for the compounds examined were determined from concentration-response curves using typically concentrations ranging from 10 nM to 10 µM. Tests against other PDE enzymes using standard methodology also showed that compounds of the invention are highly selective for the cGMP specific PDE enzyme.

-cGMP level measurements

Rat aortic smooth muscle cells (RSMC) prepared according to Chamley et al. in *Cell Tissue Res.* 177, 503-522 (1977) were used between the 10 th and 25 th passage at confluence in 24-well culture dishes. Culture media was aspirated and replaced with PBS (0.5 ml) containing the compound tested at the appropriate concentration. After 30 minutes at 37° C., particulates guanylate cyclase was stimulated by addition of ANF (100nM) for 10 minutes. At the end of incubation, the medium was withdrawn and two extractions were performed by addition of 65% ethanol (0.25 ml). The two ethanolic extracts were pooled and evaporated until dryness, using a Speed-vac system. c-GMP was measured after acetylation by scintillation proximity immunoassay (AMERSHAM).

The compounds according to the present invention were typically found to exhibit an IC₅₀ value of less than 500 nM, and an EC₅₀ value of less than 5. In vitro test data for representative compounds of the invention is given in following Table 1:

TABLE 1

Example No.	IC ₅₀ nM	EC ₅₀ µM
12	10	0.15
36	<10	0.5
52	20	0.8
63	30	0.35
79	<10	0.15
82	20	0.5
84	10	0.4
89	10	<0.1
95	2	0.2
101	10	0.3
115	<10	0.4

EXAMPLE 122

-Antihypertensive activity in rats The hypotensive effects of compounds according to the invention as identified in

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vessel patency, peripheral vascular disease, vascular disorders, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility, in a human or non-human animal body, which method comprises administering to said body a therapeutically effective amount of a compound according claim 1.

10. A pharmaceutical composition comprising a compound of the according claim 1, together with a pharmaceutically acceptable diluent or carrier therefor.

11. A process of preparing a pharmaceutical composition comprising a compound according to claim 1, which process comprises mixing said compound together with a pharmaceutically acceptable diluent or carrier therefor.

12. Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

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(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-[3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

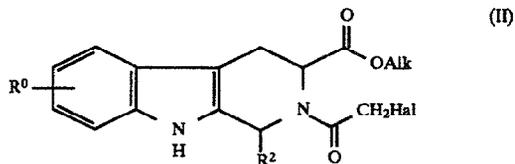
(5aR,12R,14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1'',2'':4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione;

or physiologically acceptable salts or solvates thereof.

13. (6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

or physiologically acceptable salts or solvates thereof.

14. A process of preparing a compound of formula (I), wherein R³ represents hydrogen, which process comprises treating a compound of formula (II)



in which Alk represents C₁₋₆alkyl and Hal is a halogen atom, with a primary amine R₁NH₂ or the process as hereinbefore described followed by

- i) an interconversion step; and/or either
- ii) salt formation; or
- iii) solvate formation.

15. Compounds of formulae (II).

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,859,006
DATED : January 12, 1999
INVENTOR(S) : Alain Claude-Marie Daugan

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

- Column 49, line 50, "mono-cyclic" should be --monocyclic--
- Column 50, line 12, "halo C₁₋₆alkyl" should be --haloC₁₋₆alkyl--
- Column 50, line 15, "mono-cyclic" should be --monocyclic--
- Column 50, line 24, "ben-zene" should be --benzene--
- Column 50, line 32, delete "any of"
- Column 50, line 34, "C₃₋₆ cycloalkylmethyl," should be --C₃₋₆cycloalkylmethyl--

Signed and Sealed this
Twenty-eighth Day of September, 1999

Attest:



Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

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Column 50, line 32, delete "any of"

Column 50, line 34, "C₃₋₆ cycloalkylmethyl," should be --C₃₋₆cycloalkylmethyl--



Signed and Sealed this

Twenty-eighth Day of September, 1999

Attest:

Handwritten signature of the Attesting Officer, Mary H. Allen.

Attesting Officer

Handwritten signature of Q. Todd Dickinson.

Q. TODD DICKINSON

Acting Commissioner of Patents and Trademarks

Appln. Page #	Appln. Line #	Column #	Line #	Error by
Title page	Title	Title	First column, first line	PTO
Foreign Appln. Priority Data		First page, first column	Foreign Appln. Priority Data	PTO
1	1	1	1	PTO
2	23	2	30	PTO
3	4	2	52	PTO
3	10	2	63	PTO
4	23	3	57	PTO
5	22	4	37	PTO
5	24	4	40	PTO
5	25	4	41	PTO
6	5	4	56	PTO
6	12	4 /	66	PTO
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15	34	11	45	PTO
16	19	12	3	PTO
17	2	12	30	PTO
17	26	12	65	Applicant
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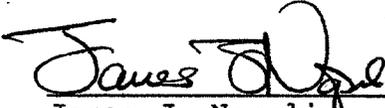
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75	18	48	33	PTO
76	5	48	66	PTO

Our check in the amount of \$100.00 to correct the error(s) by patentee(s) is submitted herewith.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 
James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
December 16, 2003

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 5,859,006
 DATED : January 12, 1999
 INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title, first column, first line, "Derivatives; Process" should be
 -- Derivatives, Process --

First page, first column, line [30], "9401090" should be
 -- 9491090.7 --

Column 1, line 1, "Derivatives; Process" should be
 -- Derivatives, Process --

Column 2, line 30, "(e.g. 1: 2 or 3)" should be -- (e.g. 1, 2 or 3) --

Column 2, line 52, "(CH₂)_a" should be -- (CH₂)_n --

Column 2, line 63, "allyl, groups" should be -- allyl groups --

Column 3, line 57, "(CH₂)_a" should be -- (CH₂)_n --

Column 4, line 37, "-6-3,4-" should be -- -6-(3,4- --

Column 4, line 40, "hexahydro6" should be -- hexahydro-6 --

Column 4, line 41, "[3, 4b]" should be -- [3, 4-b] --

MAILING ADDRESS OF SENDER:
 James J. Napoli, Ph.D.
 MARSHALL, GERSTEIN & BORUN LLP
 233 S. Wacker Drive, Suite 6300
 Sears Tower
 Chicago, Illinois 60606-6357

PATENT NO.: 5,859,006

No. of additional copies: 1

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 5,859,006
DATED : January 12, 1999
INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4, line 56, "(3-chloro4-" should be -- (3-chloro-4- --

Column 4, line 66, "pyrazino" should be -- pyrrolo --

Column 6, line 6, "allergic, asthma" should be -- allergic asthma --

Column 6, line 19, "0.5800" should be - 0.5-800 --

Column 6, line 48, "caprylictcapric" should be -- caprylic/capric --

Column 10, line 44, "C₁₋₃carboxylic" should be -- C₃₋₆carboxylic --

Column 11, line 34, "Cis and Trans" should be -- cis and trans --

Column 11, line 45, "m.p. 90-93°C." should be -- m.p.:90-93°C. --

Column 12, line 3, "(4ethoxyphenyl)" should be -- (4-ethoxyphenyl) --

Column 12, line 30, "-6arboxaldehyde" should be -- -6-carboxaldehyde --

Column 12, line 65, "(dd, 1H, H-3)3.7" should be
-- (dd, 1H, H-3); 3.7 --

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PATENT NO. : 5,859,006
 DATED : January 12, 1999
 INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 12, line 66, "(ddd, 1H, H-4)2.9" should be
 -- (ddd, 1H, H-4); 2.9 --

Column 12, line 66, "2.9(m, 1H-4);" should be -- 2.9 (m, 1H, H-4); --

Column 12, line 67, "m.p. 204°C." should be -- m.p.: 204°C. --

Column 13, line 7, "tetrahydronaphthyl6" should be
 -- tetrahydronaphthyl-6 --

Column 13, line 11, "2.7(m, 2H, CH₂Ar);" should be
 -- 2.7 (m, 4H, CH₂Ar); --

Column 13, line 12, "1.7(S, 4H, CH₂CH₂Ar)." should be
 -- 1.7 (S, 4H, CH₂CH₂Ar)."

Column 13, line 23, "(S, 3H, CO₂CH₃)3.2" should be
 -- (S, 3H, CO₂CH₃); 3.2 --

Column 13, line 25, "11 9°C" should be -- 119°C --

Column 13, line 25, "is" should be -- isomers --

MAILING ADDRESS OF SENDER:
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PATENT NO.: 5,859,006

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 5,859,006
DATED : January 12, 1999
INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13, line 29, "iso" should be -- isomers --

Column 13, line 59, "-thienyl))-" should be -- -thienyl) --

Column 14, line 44, "4-3.9(dd, 1H, H-3)3.8" should be
-- 4-3.9 (dd, 1H, H-3); 3.8 --

Column 14, line 45, "3.2-3.1(ddd, 1H, H-4)3" should be
-- 3.2-3.1 (ddd, 1H, h-4); 3 --

Column 14, line 46, "1.7(brs, 1H, NH)" should be
-- 1.7 (brs, 1H, NH) --

Column 14, line 52, "[3, 4-b[" should be -- [3, 4-b] --

Column 15, line 6, "[3, 4b]" should be -- [3, 4b] --

Column 15, line 11, "10.3(S, 1H, NH-indole)9.4" should be
-- 10.3 (S, 1H, NH-indole); 9.4 --

Column 15, line 13, "3.75(S, 3H, CO₂CH₃) 3.1" should be
-- 3.75 (S, 3H, CO₂CH₃); 3.1 --

MAILING ADDRESS OF SENDER:

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PATENT NO. : 5,859,006
 DATED : January 12, 1999
 INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 14, line 13, "3.1(m, 1H, H4);" should be -- 3.1 (m, 1H, H4); --
 Column 15, line 18, "(3-hydroxy4-" should be -- (3-hydroxy-4- --
 Column 15, line 22, "3-hydroxy4-" should be -- 3-hydroxy-4- --
 Column 15, line 44, ". . .CH₃)1.4" should be -- . . .CH₃); 1.4 --
 Column 15, line 57, "(Me)₂)2.4" should be -- (Me)₂); 2.4 --
 Column 15, line 58, "the isomer" should be -- the trans isomer --
 Column 15, line 62, "(4-nitronhenyl)" should be -- (4-nitrophenyl) --
 Column 16, line 15, "iso" should be -- isomers --
 Column 16, line 25, "tetrahydro6" should be -- tetrahydro-6 --
 Column 16, line 36, "[3, 4b]" should be -- [3', 4-b] --
 Column 16, line 43, "(dd, 1H, H-3) 3.8" should be
 -- (dd, 1H, H-3); 3.8 --

MAILING ADDRESS OF SENDER:
 James J. Napoli, Ph.D.
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 Chicago, Illinois 60606-6357

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PATENT NO. : 5,859,006
DATED : January 12, 1999
INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16, line 48, "]3, 4-b]" should be -- [3, 4-b] --

Column 17, line 26, "(3-chloro4-" should be -- (3-chloro-4 --

Column 17, line 29, "(3-chloro4-" should be -- (3-chloro-4 --

Column 19, line 49, "NA2SO4." should be -- Na₂SO₄. --

Column 20, line 36, "dropwide" should be -- dropwise --

Column 21, line 1, "4dihydro-" should be -- 4-dihydro- --

Column 22, line 21, "methylenedioxypheriyl" should be
-- methylenedioxyphenyl --

Column 22, line 26, "(0,7g," should be -- (0.7 g, --

Column 22, line 37, "4dibenzyloxyphenyl)" should be
-- 4-dibenzyloxyphenyl) --

Column 22, line 40, "4-b]indole" should be -- 4-b]indole --

MAILING ADDRESS OF SENDER:

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DATED : January 12, 1999
INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 22, line 45, "4.95 (d,2H)3.85" should be -- 4.95 (d, 2H); 3.85 --

Column 22, line 48, "(ppm) 7.6-7" should be -- (ppm): 7.6-7 --

Column 23, line 1, "-5 carboxaldehyde" should be
-- -5-carboxaldehyde --

Column 23, line 50, "2-methyl6-" should be -- 2-methyl-6 --

Column 23, line 51, "[2'1':6.1]" should be -- [2',1':6,1] --

Column 23, line 62, "hexahydro6-" should be -- hexahydro-6- --

Column 24, line 6, "fluoro6" should be -- fluoro-6 --

Column 24, line 7, "2-(2.2.2-" should be -- 2-(2,2,2- --

Column 24, line 33, "4methylenedioxyphenyl" should be
-- 4-methylenedioxyphenyl --

Column 24, line 63, "(2pyridyl)" should be -- (2-pyridyl) --

Column 26, line 8, "4b]" should be -- 4-b] --

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 26, line 38, "butyl6" should be -- butyl-6 --
Column 27, line 28, "(4-fluorobenzyl)6-" should be
-- (4-fluorobenzyl)-6- --
Column 27, line 40, "-pyrazino[[2'. . ." should be
-- pyrazino[2' . . . --
Column 27, line 58, "N, 1 1.19%." should be -- n, 11.19% --
Column 28, line 29, "[3, 4b]" should be -- [3, 4-b] --
Column 28, line 50, "benzyl6" should be -- benzyl-6 --
Column 29, line 13, "C, 70.93," should be -- C, 70.93; --
Column 29, line 17, "hexahydro6" should be -- hexahydro-6 --
Column 29, line 42, "[3, 4b]" should be -- [3, 4-b] --
Column 30, line 61, "lphenyl" should be -- 1-phenyl --

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DATED : January 12, 1999
INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 31, line 16, "pyrido3, 4-b]" should be -- pyrido[3, 4-b] --

Column 31, line 52, "naphthyl))" should be -- naphthyl) --

Column 32, line 15, "N, 1 0.77%" should be -- N, 10.77% --

Column 32, line 26, "53.01 ;" should be -- 53.01; --

Column 32, line 36, "H, 3.81 ;" should be -- H, 3.81; --

Column 32, line 64, "[2',1':6.1]" should be -- [2',1':6,1] --

Column 33, line 48, "11. 98%" should be -- 11.98% --

Column 33, line 58, "N, 1.59%" should be -- N, 11.59% --

Column 34, line 14, "C, 73.01;H, 6.84." should be
-- C; 73.01; H, 6.84; --

Column 34, line 26, "C, 71.42.H, 6.07:" should be
-- C, 71.42; H, 6.07; --

MAILING ADDRESS OF SENDER:

James J. Napoli, Ph.D.

MARSHALL, GERSTEIN & BORUN LLP

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Chicago, Illinois 60606-6357

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO. : 5,859,006
DATED : January 12, 1999
INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 34, line 52, "trifluoromethoxyphenyl" should be
-- trifluoromethoxyphenyl --

Column 37, lines 51-52, "butylamine" should be -- isobutylamine --

Column 38, line 9, "[3, 4b]" should be -- [3, 4-b] --

Column 38, lines 10-11, "cyclopentylamine" should be
-- cyclohexylmethylamine --

Column 38, line 38, "buylamine" should be -- butylamine --

Column 39, line 8, "12,a" should be -- 12a --

Column 39, line 18, "+27.60°" should be -- +27.6° --

Column 39, line 49, "7.12," should be -- 7, 12, --

Column 40, lines 34-35, "6, 1-b]pyrido-[3 . . ." should be
-- 6,1]pyrido[3 . . . --

MAILING ADDRESS OF SENDER:

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PATENT NO. : 5,859,006
DATED : January 12, 1999
INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 40, line 64, "(3,4-methylenedioxyphenyl)" should be
-- (3,4-methylenedioxyphenyl) --

Column 42, line 10, "Pyrido" should be -- pyrido --

Column 42, line 24, "Pyrido" should be -- pyrido --

Column 42, line 52, "Pyrido" should be -- pyrido --

Column 44, line 59, "EXAMPLE 1.15" should be -- EXAMPLE 115 --

Column 44, line 60, "1,2,5,6,11, . . ." should be
-- 1,2,3,5,6,11, . . ."

Column 44, line 61, "[1',2':4',5']" should be -- [1",2":4',5'] --

Column 44, line 64, "(0.8 g, 1.37 mmol)" should be
-- (0.8 g, 1.37 mmol) --

Column 45, line 34, "dimethyl6" should be -- dimethyl-6 --

Column 45, line 43, "(2,25 mL)," should be -- (2.25 mL), --

MAILING ADDRESS OF SENDER:
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DATED : January 12, 1999
INVENTOR(S) : ALAIN CLAUDE-MARIE DAUGAN

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 48, line 33, "10 th and 25 th " should be -- 10th and 25th --

Column 48, line 66, "-Antihypertensive activity in rats The hypotensive" should be
-- Antihypertensive activity in rats (New line) The hypotensive --

MAILING ADDRESS OF SENDER:
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Chicago, Illinois 60606-6357

PATENT NO.: 5,859,006

No. of additional copies: 1

ICOS CORPORATION
22021 20th Avenue S.E.
Bothell, WA 98021
+25.485.1900

November 6, 1997

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkens Avenue
Rockville, MD 20852
Attn: Lisa Rarick, M.D.
Division of Reproductive and Urologic Drug Products - HFD 580

Subject: Investigational New Drug Application
IC351 —Beta Carboline Phosphodiesterase Type 5 Inhibitor
Indication: Treatment of Male Erectile Dysfunction
Serial No. 000

Dear Dr. Rarick:

Enclosed please find, in triplicate, an Investigational New Drug Application for a Beta Carboline Phosphodiesterase Type 5 Inhibitor termed IC351. The clinical indication covered by this application is male erectile dysfunction.

IC351 is an inhibitor of the cyclic GMP-specific phosphodiesterase type 5, an enzyme also referred to in the literature as PDE5. This compound was developed during a collaboration between ICOS Corporation and Glaxo Wellcome, Ltd. As of January, 1997, ICOS Corporation has assumed sole responsibility for the continued development of this compound.

The manufacture of IC351 drug substance comprises four steps which employ standard equipment, moderate reaction conditions, and common reagents with well-defined hazards. The product is a single stereoisomer and analytical methods have been developed to distinguish among all the possible diastereomers.

Erection of the penis requires relaxation of the arterial and sinusoidal cavernous smooth muscle, thereby entrapping blood within the sinuses and restricting cavernous output. This requires both neuronal stimulation and vasoactive mediator release. It is believed that nitric oxide (NO), an endothelium-derived relaxing factor (EDRF), plays a central role in this process. NO is an endogenous regulatory substance that relaxes smooth muscle by stimulating guanylyl cyclase, which in turn causes increases in cyclic guanosine monophosphate (cGMP). In many cell types, including cavernosal smooth muscle, phosphodiesterase Type 5, or PDE5, appears to be the major enzyme responsible for the hydrolysis of cGMP. A compound that inhibits PDE5 will prevent cGMP catabolism, thereby potentiating the relaxant effects of substances that increase cGMP in vascular smooth

Lisa Rarick, M.D.

Page 2

November 6, 1997

muscle, such as NO. The aim of the drug development program supporting this study was, therefore, to find a potent and specific inhibitor of PDE5. Such a compound should facilitate the achievement and maintenance of erection by enhancing smooth muscle relaxation, leading to increased blood flow to the penis.

In cultured cells, IC351 increased the level of cGMP in the presence of agents that activate guanylyl cyclase. Furthermore, in the presence of a functional endothelium, IC351 was shown to relax rat aortic rings that had been precontracted with phenylephrine. When administered orally to hypertensive rats, IC351 lowered blood pressure without affecting heart rate. This effect was long-lasting, and not subject to the development of tolerance on repeated administration. In both rats and dogs, orally administered IC351 produced no findings that precludes continued clinical evaluation in humans.

Three Phase I studies have been conducted by Glaxo Wellcome, Ltd. (Clinical Reports for Protocols C95-031, C95-050, and C95-064 are appended in Item 9 of this submission). In these three studies, forty-four subjects were exposed to IC351 and twenty-nine to placebo. No serious adverse events associated with IC351 were reported. The most commonly reported adverse event was headache, with several subjects reporting severe back pain as well. The relationship of these adverse events to drug is unclear but cannot be excluded at this time.

We propose to continue the clinical evaluation of IC351 with an initial study in male erectile dysfunction. Protocol DSD03, entitled "A Double-Blind, Placebo-Controlled Safety and Efficacy Study of Twenty-one Days of Once Daily Treatment with IC351 in Patients with Mild to Moderate Erectile Dysfunction" is submitted in this initial IND. The purpose of this study is to (1) assess the safety and tolerability to four strengths of IC351 in erectile dysfunction patients exposed to daily dosing for 21 days, and to determine (2) an initial indication of efficacy in patients with mild to moderate male erectile dysfunction, (3) the steady state plasma level dose proportionality of four oral strengths of IC351, and (4) develop insight into the dose-response relationship of efficacy in treating erectile dysfunction. We propose to enroll three hundred patients in this multi-center study. The expected study duration is 3 months.

Investigator documentation for Harin Padma-Nathan, M.D., the Principal Investigator, is included in Item 6 of this submission.

If you have any questions or comments regarding this submission, please contact me at (206) 485-1900 extension 2297.

Sincerely,



Jeff Hesselberg, MBA
Associate Director, Regulatory Affairs

Food and Drug Administration
Rockville MD 20857

IND 54,553

ICOS Corporation
22021 20th Ave S.E.
Bothell, WA 98021

NOV 17 1997

Dear Mr. Hesselberg:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 54,553

Sponsor: ICOS Corporation

Name of Drug: IC351 Beta Carboline Phosphodiesterase Type 5 Inhibitor

Date of Submission: November 6, 1997

Date of Receipt: November 10, 1997

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of information; reporting any unexpected fatal or life-threatening experience to FDA by telephone no later than three working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

IND 54,553

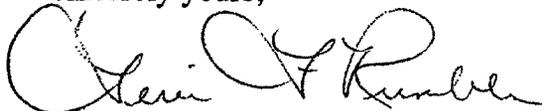
Page 2

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this submission, please contact me at (301) 827-4260.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Terri Rumble". The signature is fluid and cursive, with a large initial "T" and "R".

Terri Rumble B.S.
Project Manager
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center of Drug Evaluation and Research

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Health Service

IND 54,553

U.S. Food & Drug Administration
Washington, DC 20857

ICOS Corporation
Attention: Mr. Jeff Hesselberg, M.B.A.
22021 20th Avenue, S.E.
Bothell, Washington 98021

JUL 29 1997

Dear Mr. Hesselberg:

Please refer to your Investigational New Drug Application (IND) submitted November 6, 1997, pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for IC351 (Beta Carboline Phosphodiesterase Type 5 Inhibitor).

We also refer to your submissions dated December 15, 1997, March 13, April 24, May 21 and July 3, 1998, which provided a full response to our December 16, 1997, letter, which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues.

We have completed the review of your submissions, and have concluded that it is reasonably safe to initiate clinical trials.

You are reminded that the study report for Protocol DSD06 should be submitted prior to proceeding with any additional U.S. clinical studies.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any unexpected fatal or life-threatening experiences by telephone no later than three working-days after receipt of the information; reporting reactions that are both serious and unexpected in writing within ten working days of receipt of the information (21 CFR 312.32) and submitting progress reports at least annually (21 CFR 312.33).

If you have any questions concerning this IND, please contact Terri Rumble, Project Manager, at 301-827-4260.

Sincerely,

Lisa D. Rarick, M.D.

Director

Division of Reproductive and

Urologic Drug Products (HFD-580)

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Lilly ICOS LLC
c/o
Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285

June 28, 2001

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Original Application, NDA 21368

Re: NDA 21368, Cialis (IC351, tadalafil) – Initial Submission

This letter accompanies submission of an original New Drug Application (NDA) for Cialis, a PDE5 inhibitor, for the indication of erectile dysfunction. This NDA is submitted in electronic format according to the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs." As specified in this Guidance, a paper review copy containing 115 volumes is included in this submission. As discussed in a teleconference between Dornette Spell-LeSané (FDA) and Susan Sullivan (Lilly ICOS), four paper desk copies of volume 1.1 are also provided.

Substantial evidence of effectiveness supporting the use of Cialis for the treatment of erectile dysfunction is provided in the enclosed application based on six primary randomized, double blind, placebo-controlled studies (LV DJ, LVCO, LV CQ, LV BK, LV BE, and LV BN).

Lilly ICOS has met with FDA personnel on a number of occasions to discuss the development program for Cialis since ICOS Corporation's filing the IND for this drug on November 6, 1997. The interactions and agreements from those meeting are outlined in the Application Summary, H.2.1, Regulatory History and Agreements.

The complete NDA is provided in electronic format on digital tape. The submission size is approximately 3.3 gigabytes. All electronic media have been checked by representatives of Lilly ICOS Information Technology and have been verified to be free of known viruses. The virus checking software was McAfee VirusScan version 4.0.2 using Virus Definitions 4.0.4136 created on 2 May 2001.

The User Fee of \$309,647.00 for this submission has been paid under User Fee number 4124. Form 3397 has been provided.

A Debarment Certification has been provided.

Reference is made to the agreement between FDA and Lilly ICOS with respect to the reporting of financial information for investigators who participated in the pivotal efficacy and bioequivalence trials. This agreement is summarized in the Regulatory History and Agreements section of the Application Summary of this NDA. Forms 3454 and 3455 have been provided along with accompanying information as requested by FDA.

To co-ordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications, concerning this file, regardless of subject, be directed to:

Gregory T. Brophy, Ph.D.
Director
U. S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

FAX number: (317) 433-2255

Any calls regarding this submission should be made to:

Catherine A. Melfi, Ph.D.
(317) 277-2905 (work)
(317) 843-2369 (home)

or alternatively you may reach Dr. Melfi via E-mail at melfi@lilly.com.

In the case of Dr. Melfi's absence please contact:

Susan Sullivan
(425) 415-5649 (work)
(425) 379-9698 (home)

You may also contact:

Gregory T. Brophy, Ph.D.
(317) 277-3799 (work)
(317) 335-7360 (home)

Any calls relating to functionality of the electronic portion of the submission should be made to:

Patrick Q. Mooney
(317) 276-0586 (work)
(317) 272-5528 (home)
(317) 331-3096 (cell phone)

On holidays, Saturdays, or Sundays, call Dr. Melfi, Ms. Sullivan, or Dr. Brophy at home using the telephone numbers indicated.

Close liaison between the representatives of Lilly ICOS listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Sincerely,

Lilly Research Laboratories on behalf of Lilly ICOS LLC



Gregory T. Brophy, Ph.D.
Director
U. S. Regulatory Affairs

Enclosures

cc: **4 Desk copies:** volume 1.1 only
Ms. Dornette Spell-LeSane



NDA 21-368

Lilly ICOS
Attention: Gregory Brophy, Ph.D.
Director
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

FILE COPY

Dear Dr. Brophy:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Cialis (IC351, tadalafil) 20 mg tablets
Review Priority Classification:	Standard (S)
Date of Application:	June 28, 2001
Date of Receipt:	June 29, 2001
Our Reference Number:	NDA 21-368

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 28, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 29, 2001 and the secondary user fee goal date will be June 29, 2002.

Be advised that, as of April 1, 1999, 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 (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a

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"Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Dornette Spell-LeSane, NP-C
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-368

Lilly ICOS LLC
Attention: Catherine Melfi, Ph.D.
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi:

Please refer to your new drug application dated June 28, 2001, received June 29, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cialis® (tadalafil), tablets 5mg, 10mg and 20mg.

We acknowledge receipt of your submissions dated June 28, July 24, August 27, September 10, 17, 18, and 25, October 1, 22, 25, and 30, November 5, and December 6, 2001; January 14 and 23, February 1, 6, 26, and 28, March 4, 6, 12, 18, 20, 22, and 25, April 1, 4, 5, and 16, May 10 (2), 14, 16, 24, and 30, June 6, 13, and 28, August 6, 8, 22, and 26, September 5, 12, 24, and 30, November 15 and 27, 2002, February 13, April 16 and 24, May 16, 27, and 30, June 5, 17, 24, and 26, July 15 and 22, August 7, 11, 19, and 29, September 11, October 9, 14, 15, 20 (2), and 24 (2), and November 5, 11, 12, 17, 19, and 20, 2003.

The May 27, 2003 submission constituted a complete response to our April 29, 2002 action letter.

This new drug application provides for the use of Cialis® (tadalafil) tablets for the treatment of erectile dysfunction.

We completed our review of this application, as amended. It is 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, text for the patient package insert). 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 this submission "FPL for approved NDA 21-368." Approval of this submission by FDA is not required before the labeling is used.