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(71) Applicant *(for all designated States except US)*: LILLY ICOS LLC [US/US]; 1209 Orange Street, Wilmington, DE 19801 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PULLMAN, William, Ernest [US/US]; 3004 Towne Drive, Carmel, IN 46032 (US). WHITAKER, John, Steven [US/US]; 19340 162nd Avenue, Woodinville, WA 98072 (US).

(74) Agent: NAPOLI, James, J.; Marshall, O'Toole, Gerstein, Murray & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago, IL 60606 (US).

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(54) Title: UNIT DOSAGE FORM

(57) Abstract

The present invention relates to highly selective phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manufacture. In particular, the present invention relates to potent inhibitors of cyclic guanosine 3',5'–monophosphate specific phosphodiesterase type 5 (PDE5) that when incorporated into a pharmaceutical product at about 1 to about 20 mg unit dosage are useful for the treatment of sexual dysfunction.

FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **29342/36206A**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): **10/031556**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/11129	**26 April 2000**	**30 April 1999**

TITLE OF INVENTION
UNIT DOSAGE FORM

APPLICANT(S) FOR DO/EO/US
PULLMAN, William Ernest and WHITAKER, John Steven

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Return receipt postcard

PCTUS1/REV03

531 Rec'd PCT/P 19 OCT 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR) 10/051556	INTERNATIONAL APPLICATION NO. PCT/US00/11129	ATTORNEY'S DOCKET NUMBER 29342/36206A

24. The following fees are submitted:.	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	17 - 20 =	0	x $18.00	**$0.00**	
Independent claims	2 - 3 =	0	x $84.00	**$0.00**	
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$890.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**	
SUBTOTAL =				**$890.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
TOTAL NATIONAL FEE =				**$890.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
TOTAL FEES ENCLOSED =				**$890.00**	
				Amount to be: refunded	$
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a. ☒ A check in the amount of **$890.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

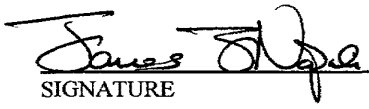
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **13-2855** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

NAPOLI, James J.
Customer No. 04743
Marshall, Gerstein & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
United States of America



SIGNATURE

James J. Napoli

NAME

32,361

REGISTRATION NUMBER

19 October 2001

DATE

PATENT

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants:	"EXPRESS MAIL" mailing label No. **EK657817671US**
WILLIAM E. PULLMAN ET AL.	
U.S. National Phase of PCT/US00/11129 filed April 26, 2000	Date of Deposit: **October 19, 2001**
Filed: Herewith	I hereby certify that this paper (or fee) is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 CFR §1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.
For: **UNIT DOSAGE FORM**	
Group Art Unit: Unassigned	
Examiner: Unassigned	
Attorney Docket No. 29342/36206A	Richard Zimmermann

PRELIMINARY AMENDMENT
ACCOMPANYING APPLICATION TRANSMITTAL

Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend the above-identified application as follows:

IN THE SPECIFICATION:

Page 1, after the title, please delete the CROSS-REFERENCE TO RELATED APPLICATION in its entirety and insert therefor:

--CROSS-REFERENCE TO RELATED APPLICATIONS

This is the U.S. national phase application of International Application No. PCT/US00/11129, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/132,036, filed April 30, 1999.--

IN THE CLAIMS:

Cancel claims 18 and 19 without prejudice.

Amend claims 7-9 as follows:

7. (Amended) The dosage form of claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

8. (Amended) The dosage form of claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in the form of a tablet.

9. (Amended) (Amended) The dosage form of claim 1, 2, 3, 4, 5, or 6 for use in treating a condition wherein inhibition of PDE5 is desirable.

REMARKS

Claims 1-19 are pending in the application. Claims 18 and 19 have been cancelled. Therefore, claims 1-17 are at issue in this application.

The amendments are described in more detail below. Pursuant to 37 C.F.R. §1.121, a marked-up version of the changes made to the claims by the present amendment is attached hereto following the signature page of this amendment. The first page of the marked-up version of the changes is captioned "Version With Markings to Show Changes Made."

This preliminary amendment adds no new matter. The specification has been amended to insert a cross-reference to a related application. Claims 7-9 have been amended to improve the form of the claims.

It is submitted that the amendment should be entered, and that the claims are of a proper form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

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
October 19, 2001

Version With Markings to Show Changes Made
(U.S. National Stage of PCT/US00/11129
filed October 19, 2001)

IN THE SPECIFICATION:

The following cross-reference to related application has been inserted into the specification:

CROSS-REFERENCE TO RELATED APPLICATIONS

This is the U.S. national phase application of International Application No. PCT/US00/11129, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/132,036, filed April 30, 1999.

IN THE CLAIMS:

Claims 18 and 19 have been cancelled without prejudice.

Claims 7-9 have been amended as follows:

7. (Amended) The dosage form of [claims 1 through 6] claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

8. (Amended) The dosage form of [claims 1 through 6] claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in the form of a tablet.

9. (Amended) The dosage form of [claims 1 through 6] claim 1, 2, 3, 4, 5, or 6 for use in treating a condition wherein inhibition of PDE5 is desirable.

UNIT DOSAGE FORM

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of provisional patent application Serial No. 60/132,036, filed April 30, 1999.

FIELD OF THE INVENTION

The present invention relates to a highly selective phosphodiesterase (PDE) enzyme inhibitor and to its use in a pharmaceutical unit dosage form. In particular, the present invention relates to a potent inhibitor of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase type 5 (PDE5) that when incorporated into a pharmaceutical product is useful for the treatment of sexual dysfunction. The unit dosage form described herein is characterized by selective PDE5 inhibition, and accordingly, provides a benefit in therapeutic areas where inhibition of PDE5 is desired, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes.

BACKGROUND OF THE INVENTION

The biochemical, physiological, and clinical effects of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE) inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or

endocrine function is desired. Type 5 cGMP-specific phosphodiesterase (PDE5) is the major cGMP hydrolyzing enzyme in vascular smooth muscle, and its expression in penile corpus cavernosum has been reported (Taher et al., *J. Urol., 149*, p. 285A (1993)). Thus, PDE5 is an attractive target in the treatment of sexual dysfunction (Murray, *DN&P 6(3)*, pp. 150-56 (1993)).

A pharmaceutical product, which provides a PDE5 inhibitor, is currently available and marketed under the trademark VIAGRA®. The active ingredient in VIAGRA® is sildenafil. The product is sold as an article of manufacture including 25, 50, and 100 mg tablets of sildenafil and a package insert. The package insert provides that sildenafil is a more potent inhibitor of PDE5 than other known phosphodiesterases (greater than 80 fold for PDE1 inhibition, greater than 1,000 fold for PDE2, PDE3, and PDE4 inhibition). The IC_{50} for sildenafil against PDE5 has been reported as 3 nM (*Drugs of the Future, 22(2)*, pp. 138-143 (1997)) and as 3.9 nM (Boolel et al., *Int. J. of Impotence, 8*, pp. 47-52 (1996)). Sildenafil is described as having a 4,000-fold selectivity for PDE5 versus PDE3, and only a 10-fold selectivity for PDE5 versus PDE6. Its relative lack of selectivity for PDE6 is theorized to be the basis for abnormalities related to color vision.

While sildenafil has obtained significant commercial success, it has fallen short due to its significant adverse side effects, including facial flushing (10% incidence rate). Adverse side effects limit the use of sildenafil in patients suffering from vison abnormalities, hypertension, and, most

significantly, by individuals who use organic nitrates (Welds et al., *Amer. J. of Cardiology, 83(5A)*, pp. 21(C)-28(C) (1999)).

The use of sildenafil in patients taking organic nitrates causes a clinically significant drop in blood pressure which could place the patient in danger. Accordingly, the package label for sildenafil provides strict contraindications against its use in combination with organic nitrates (e.g., nitroglycerin, isosorbide mononitrate, isosorbide nitrate, erythrityl tetranitrate) and other nitric oxide donors in any form, either regularly or intermittently, because sildenafil potentiates the hypotensive effects of nitrates. See C.R. Conti et al., *Amer. J. of Cardiology, 83(5A)*, pp. 29C-34C (1999). Thus, even with the availability of sildenafil, there remains a need to identify improved pharmaceutical products that are useful in treating sexual dysfunction.

Daugan U.S. Patent 5,859,006 discloses certain tetracyclic derivatives that are potent inhibitors of cGMP-specific PDE, or PDE5. The IC_{50} of the compounds disclosed in U.S. Patent No. 5,859,006 is reported in the range of 1 nM to 10 µM. The oral dosage for such compounds is 0.58 mg daily for an average adult patient (70 kg). Thus, unit dosage forms (tablets or capsules) are reported as 0.2 to 400 mg of active compound. Significant adverse side effects attributed to compounds disclosed in U.S. Patent No. 5,859,006 are not disclosed.

Applicants have discovered that one such tetracyclic derivative, (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, alternatively named (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, and referred to herein as Compound (I), can be administered in a unit dose that provides an effective treatment without the side effects associated with the presently marketed PDE5 inhibitor, sildenafil. Prior to the present invention such side effects were considered inherent to the inhibition of PDE5.

Significantly, applicants' clinical studies also reveal that an effective product having a reduced tendency to cause flushing in susceptible individuals can be provided. Most unexpectedly, the product also can be administered with clinically insignificant side effects associated with the combined effects of a PDE5 inhibitor and an organic nitrate. Thus, the contraindication once believed necessary for a product containing a PDE5 inhibitor is unnecessary when Compound (I) is administered as a unit dose of about 1 to about 20 mg, as disclosed herein. Thus, the present invention provides an effective therapy for sexual dysfunction in individuals who previously were untreatable or suffered from unacceptable side effects, including individuals having cardiovascular disease, such as in individuals requiring nitrate therapy, having suffered a myocardial infarction more than three months before the onset of sexual dysfunction therapy, and suffering from class 1 congestive heart failure, or individuals suffering from vision abnormalities.

The present invention provides Compound (I) in a unit dosage form. That is, the present invention provides a pharmaceutical unit dosage form suitable for oral administration comprising about 1 to about 20 mg Compound (I).

SUMMARY OF THE INVENTION

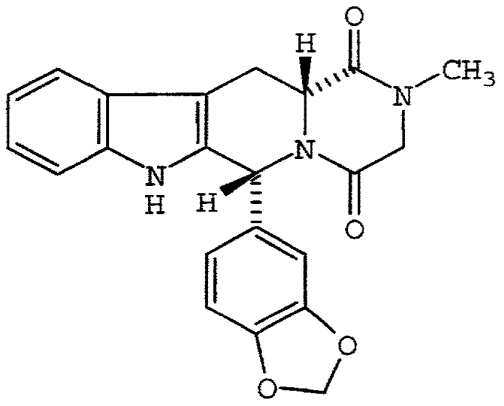
The present invention provides a pharmaceutical dosage form for human pharmaceutical use, comprising about 1 to about 20 mg of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione in a unit dosage form suitable for oral administration.

The present invention further provides a method of treating conditions where inhibition of PDE5 is desired, which comprises administering to a patient in need thereof an oral dosage form containing about 1 to about 20 mg of a selective PDE5 inhibitor, as needed, up to a total dose of 20 mg per day. The invention further provides the use of an oral dosage form comprising a selective PDE5 inhibitor at a dosage of about 1 to about 20 mg for the treatment of sexual dysfunction.

Specific conditions that can be treated by the present invention, include, but are not limited to, male erectile dysfunction and female sexual dysfunction, particularly female arousal disorder, also known as female sexual arousal disorder.

In particular, the present invention is directed to a pharmaceutical unit dosage composition

comprising about 1 to about 20 mg of a compound having the structural formula:



said unit dosage form suitable for oral administration, and method of treating sexual dysfunction using the pharmaceutical unit dose composition.

DETAILED DESCRIPTION

For purposes of the present invention as disclosed and described herein, the following terms and abbreviations are defined as follows.

The term "container" means any receptacle and closure therefor suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

The term "IC_{50}" is the measure of potency of a compound to inhibit a particular PDE enzyme (e.g., PDE1c, PDE5, or PDE6). The IC_{50} is the concentration of a compound that results in 50% enzyme inhibition in a single dose-response experiment. Determining the IC_{50} value for a compound is readily

carried out by a known *in vitro* methodology generally described in Y. Cheng et al., *Biochem. Pharmacol., 22*, pp. 3099-3108 (1973).

The term "package insert" means information accompanying the product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

The term "oral dosage form" is used in a general sense to reference pharmaceutical products administered orally. Oral dosage forms are recognized by those skilled in the art to include such forms as liquid formulations, tablets, capsules, and gelcaps.

The term "vision abnormalities" means abnormal vision characterized by blue-green vision believed to be caused by PDE6 inhibition.

The term "flushing" means an episodic redness of the face and neck attributed to vasodilation caused by ingestion of a drug, usually accompanied by a feeling of warmth over the face and neck and sometimes accompanied by perspiration.

The term "free drug" means solid particles of drug not intimately embedded in a polymeric coprecipitate.

The presently claimed dosage form preferably is packaged as an article of manufacture for human pharmaceutical use, comprising a package insert, a container, and a dosage form comprising about 1 to about 20 mg of Compound (I)

The package insert provides a description of how to administer a pharmaceutical product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding the use of the product. The package insert generally is regarded as the label of the pharmaceutical product. The package insert incorporated into the article of manufacture indicates that Compound (I) is useful in the treatment of conditions wherein inhibition of PDE5 is desired. The package insert also provides instructions to administer one or more about 1 to about 20 mg unit dosage forms as needed, up to a maximum total dose of 20 mg per day. Preferably, the dose administered is about 5 to about 20 mg/day, more preferably about 5 to about 15 mg/day. Most preferably, a 10 mg dosage form is administered once per day.

Preferred conditions to be treated include sexual dysfunction (including male erectile dysfunction; and female sexual dysfunction, and more preferably female arousal disorder (FAD)). The preferred condition to be treated is male erectile dysfunction.

Significantly, the package insert supports the use of the product to treat sexual dysfunction in patients suffering from a retinal disease, for example, diabetic retinopathy or retinitis pigmentosa, or in patients who are using organic nitrates. Thus, the package insert preferably is free of contraindications associated with these conditions, and particularly the administration of the dosage form with an organic nitrate. More

preferably, the package insert also is free of any cautions or warnings both associated with retinal diseases, particularly retinitis pigmentosa, and associated with individuals prone to vision abnormalities. Preferably, the package insert also reports incidences of flushing below 2%, preferably below 1%, and most preferably below 0.5%, of the patients administered the dosage form. The incidence rate of flushing demonstrates marked improvement over prior pharmaceutical products containing a PDE5 inhibitor.

The container used in the article of manufacture is conventional in the pharmaceutical arts. Generally, the container is a blister pack, foil packet, glass or plastic bottle and accompanying cap or closure, or other such article suitable for use by the patient or pharmacist. Preferably, the container is sized to accommodate 1-1000 solid dosage forms, preferably 1 to 500 solid dosage forms, and most preferably, 5 to 30 solid dosage forms.

Oral dosage forms are recognized by those skilled in the art to include, for example, such forms as liquid formulations, tablets, capsules, and gelcaps. Preferably the dosage forms are solid dosage forms, particularly, tablets comprising about 1 to about 20 mg of Compound (I). Any pharmaceutically acceptable excipients for oral use are suitable for preparation of such dosage forms. Suitable pharmaceutical dosage forms include coprecipitate forms described, for example, in Butler U.S. Patent No. 5,985,326, incorporated herein by reference. In preferred embodiments, the unit dosage form of the

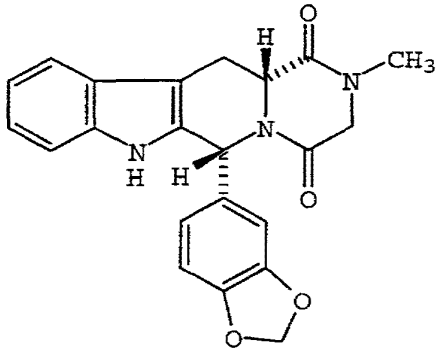
present invention is a solid free of a coprecipitate form of Compound (I), but rather contains solid Compound (I) as a free drug.

Preferably, the tablets comprise pharmaceutical excipients generally recognized as safe such as lactose, microcrystalline cellulose, starch, calcium carbonate, magnesium stearate, stearic acid, talc, and colloidal silicon dioxide, and are prepared by standard pharmaceutical manufacturing techniques as described in *Remington's Pharmaceutical Sciences, 18th Ed.*, Mack Publishing Co., Easton, PA (1990). Such techniques include, for example, wet granulation followed by drying, milling, and compression into tablets with or without film coating; dry granulation followed by milling, compression into tablets with or without film coating; dry blending followed by compression into tablets, with or without film coating; molded tablets; wet granulation, dried and filled into gelatin capsules; dry blend filled into gelatin capsules; or suspension and solution filled into gelatin capsules. Generally, the solid dosage forms have identifying marks which are debossed or imprinted on the surface.

The present invention is based on detailed experiments and clinical trials, and the unexpected observations that side effects previously believed to be indicative of PDE5 inhibition can be reduced to clinically insignificant levels by the selection of a compound and unit dose. This unexpected observation enabled the development of a unit dosage form that incorporates Compound (I) in about 1 to about 20 mg per unit dosage forms that, when orally administered, minimizes undesirable side effects previ-

ously believed unavoidable. These side effects include facial flushing, vision abnormalities, and a significant decrease in blood pressure, when Compound (I) is administered alone or in combination with an organic nitrate. The minimal effect of Compound (I), administered in about 1 to about 20 mg unit dosage forms, on PDE6 also allows the administration of a selective PDE5 inhibitor to patients suffering from a retinal disease, like diabetic retinopathy or retinitis pigmentosa.

Compound (I) has the following structural formula:



(I)

The compound of structural formula (I) was demonstrated in human clinical studies to exert a minimal impact on systolic blood pressure when administered in conjunction with organic nitrates. By contrast, sildenafil demonstrates a four-fold greater decrease in systolic blood pressure over a placebo, which leads to the contraindications in the VIAGRA® insert, and in warnings to certain patients.

The following illustrates the PDE5 and PDE6 IC_{50} values for the compound of structural

formula (I) determined by the procedures described herein.

Compound	PDE5 IC_{50} (nM)	PDE6 IC_{50} (nM)	PDE6/PDE5
I	2.5	3400	1360

The compound of structural formula (I) additionally demonstrates an IC_{50} against PDE1c of 10,000, and a ratio of PDE1c/PDE5 of 4,000.

PREPARATIONS

Human PDE5 Preparation

Recombinant production of human PDE5 was carried out essentially as described in Example 7 of U.S. Patent No. 5,702,936, incorporated herein by reference, except that the yeast transformation vector employed, which is derived from the basic ADH2 plasmid described in V. Price et al., *Methods in Enzymology*, 1985, pages 308-318 (1990), incorporated yeast ADH2 promoter and terminator sequences rather than ADH1 promoter and terminator sequences and the *Saccharomyces cerevisiase* host was the protease-deficient strain BJ2-54 deposited on August 31, 1998 with the American Type Culture Collection, Manassas, Virginia, under accession number ATCC 74465. Transformed host cells were grown in 2X SC-leu medium, pH 6.2, with trace metals, and vitamins. After 24 hours, YEP medium containing glycerol was added to a final concentration of 2X YEP/3% glycerol. Approximately 24 hours later, cells were harvested, washed, and stored at -70°C.

Cell pellets (29 g) were thawed on ice with an equal volume of lysis buffer (25 mM Tris-Cl, pH 8, 5 mM $MgCl_2$, 0.25 mM dithiothreitol, 1 mM benzamidine, and 10 µM $ZnSO_4$). Cells were lysed in a microfluidizer with N_2 at 20,000 psi. The lysate was centrifuged and filtered through 0.45 µm disposable filters. The filtrate was applied to a 150 mL column of Q Sepharose Fast Flow (Pharmacia). The column was washed with 1.5 volumes of Buffer A (20 mM Bis-Tris Propane, pH 6.8, 1 mM $MgCl_2$, 0.25 mM dithiothreitol, 10 µM $ZnSO_4$) and eluted with a step gradient of 125 mM NaCl in Buffer A followed by a linear gradient of 125-1000 mM NaCl in Buffer A.

Active fractions from the linear gradient were applied to a 180 mL ceramic hydroxyapatite column in Buffer B (20 mM Bis-Tris Propane (pH 6.8), 1 mM $MgCl_2$, 0.25 mM dithiothreitol, 10 µM $ZnSO_4$, and 250 mM KCl). After loading, the column was washed with 2 volumes of Buffer B and eluted with a linear gradient of 0-125 mM potassium phosphate in Buffer B. Active fractions were pooled, precipitated with 60% ammonium sulfate, and resuspended in Buffer C (20 mM Bis-Tris Propane, pH 6.8, 125 mM NaCl, 0.5 mM dithiothreitol, and 10 µM $ZnSO_4$). The pool was applied to a 140 mL column of Sephacryl S-300 HR and eluted with Buffer C. Active fractions were diluted to 50% glycerol and stored at -20°C. The resultant preparations were about 85% pure by SDS-PAGE.

Assay for PDE Activity

Activity of PDE5 can be measured by standard assays in the art. For example, specific

activity of any PDE can be determined as follows. PDE assays utilizing a charcoal separation technique were performed essentially as described in Loughney et al., (1996), *The Journal of Biological Chemistry, 271*:796-806. In this assay, PDE5 activity converts [^{32}P]cGMP to [^{32}P]5'GMP in proportion to the amount of PDE5 activity present. The [^{32}P]5'GMP then is quantitatively converted to free [^{32}P] phosphate and unlabeled adenosine by the action of snake venom 5'-nucleotidase. Hence, the amount of [^{32}P] phosphate liberated is proportional to enzyme activity. The assay is performed at 30 C in a 100 µL reaction mixture containing (final concentrations) 40 mM Tris-Cl (pH 8.0), 1 µM $ZnSO_4$, 5 mM $MgCl_2$, and 0.1 mg/mL bovine serium albumin. PDE5 is present in quantities that yield <30% total hydrolysis of substrate (linear assay conditions). The assay is initiated by addition of substrate (1 mM [^{32}P]cGMP), and the mixture is incubated for 12 minutes. Seventy-five (75) µg of *Crotalus atrox* venom then is added, and the incubation is continued for 3 more minutes (15 minutes total). The reaction is stopped by addition of 200 mL of activated charcoal (25 mg/-mL suspension in 0.1 M NaH_2PO_4, pH 4). After centrifugation (750 x g for 3 minutes) to sediment the charcoal, a sample of the supernatant is taken for radioactivity determination in a scintillation counter and the PDE5 activity is calculated. The preparations had specific activities of about 3 µmoles cGMP hydrolyzed per minute per milligram protein.

Bovine PDE6 Preparation

Bovine PDE6 was supplied by Dr. N. Virmaux, INSERM U338, Strasbourg. Bovine retinas were prepared as described by Virmaux et al., *FEBS Letters, 12(6)*, pp. 325-328 (1971) and see also, A. Sitaramayya et al., *Exp. Eye Res., 25*, pp. 163-169 (1977). Briefly, unless stated otherwise, all operations were done in the cold and in dim red light. Eyes were kept in the cold and in the dark for up to four hours after slaughtering.

Preparation of bovine retinal outer segment (ROS) basically followed procedures described by Schichi et al., *J. Biol. Chem., 224*:529 (1969). In a typical experiment, 35 bovine retinas were ground in a mortar with 35 mL 0.066 M phosphate buffer, pH 7.0, made up to 40% with sucrose, followed by homogenization in a Potter homogenizer (20 up and down strokes). The suspension was centrifuged at 25,000 x g for 20 minutes. The pellet was homogenized in 7.5 mL 0.006 M phosphate buffer (40% in sucrose), and carefully layered under 7.5 mL of phosphate buffer (containing no sucrose). Centrifugation was conducted in a swing-out rotor at 45,000 x g for 20 minutes, and produced a pellet which is black at the bottom, and also a red band at the interface 0.066 M. phosphate--40% sucrose/0.066 M phosphate (crude ROS). The red material at the interface was removed, diluted with phosphate buffer, spun down to a pellet, and redistributed in buffered 40% sucrose as described above. This procedure was repeated 2 or 3 times until no pellet was formed. The purified ROS was washed in phosphate

buffer and finally spun down to a pellet at 25,000 x g for 20 minutes. All materials were then kept frozen until used.

Hypotonic extracts were prepared by suspending isolated ROS in 10 mM Tris-Cl pH 7.5, 1 mM EDTA, and 1 mM dithioerythritol, followed by centrifugation at 100,000 x g for 30 minutes.

The preparation was reported to have a specific activity of about 35 nmoles cGMP hydrolyzed per minute per milligram protein.

PDE1c Preparation from *Spodoptera fugiperda* Cells (Sf9)

Cell pellets (5g) were thawed on ice with 20ml of Lysis Buffer (50mM MOPS pH 7.4, 10µM $ZnSO_4$, 0.1mM $CaCl_2$, 1mM DTT, 2mM benzamidine HCl, 5µg/ml each of pepstatin, leupeptin, and aprotenin). Cells were lysed by passage through a French pressure cell (SLM-Aminco) while temperatures were maintained below 10°C. The resultant cell homogenate was centrifuged at 36,000 rpm at 4°C for 45 minutes in a Beckman ultracentrifuge using a Type TI45 rotor. The supernatant was discarded and the resultant pellet was resuspended with 40 ml of Solubilization Buffer (Lysis Buffer containing 1M NaCl, 0.1M $MgCl_2$, 1mM $CaCl_2$, 20µg/ml calmodulin, and 1% Sulfobetaine SB12 (Z3-12) by sonicating using a VibraCell tuner with a microtip for 3 x 30 seconds. This was performed in a crushed ice/salt mix for cooling. Following sonication, the mixture was slowly mixed for 30 minutes at 4°C to finish solubilizing membrane bound proteins. This mixture was centrifuged

in a Beckman ultracentrifuge using a type TI45 rotor at 36,000 rpm for 45 minutes. The supernatant was diluted with Lysis Buffer containing 10µg/ml calpain inhibitor I and II. The precipitated protein was centrifuged for 20 minutes at 9,000 rpm in a Beckman JA-10 rotor. The recovered supernatant then was subjected to Mimetic Blue AP Agarose Chromatography.

In order to run the Mimetic Blue AP Agarose Column, the resin initially was shielded by the application of 10 bed volumes of 1% polyvinyl-pyrrolidine (i.e., MW of 40,000) to block nonspecific binding sites. The loosely bound PVP-40 was removed by washing with 10 bed volumes of 2M NaCl, and 10 mM sodium citrate pH 3.4. Just prior to addition of the solubilized PDE1c3 sample, the column was equilibrated with 5 bed volumes of Column Buffer A (50 mM MOPS pH 7.4, 10µM $ZnSO_4$, 5mM $MgCl_2$, 0.1 mM $CaCl_2$, 1 mM DTT, 2 mM benzamidine HCl).

The solubilized sample was applied to the column at a flow rate of 2 ml/min with recycling such that the total sample was applied 4 to 5 times in 12 hours. After loading was completed, the column was washed with 10 column volumes of Column Buffer A, followed by 5 column volumes of Column Buffer B (Column Buffer A containing 20 mM 5'-AMP), and followed by 5 column volumes of Column Buffer C (50 mM MOPS pH 7.4, 10 µM $ZnSO_4$, 0.1 mM $CaCl_2$, 1 mM dithiothreitol, and 2 mM benzamidine HCl). The enzyme was eluted into three successive pools. The first pool consisted of enzyme from a 5 bed volume wash with Column Buffer C containing 1 mM cAMP. The second pool consisted of enzyme from a 10 bed volume wash with Column Buffer C containing 1 M NaCl. The

final pool of enzyme consisted of a 5 bed volume wash with Column Buffer C containing 1 M NaCl and 20 mM cAMP.

The active pools of enzyme were collected and the cyclic nucleotide removed via conventional gel filtration chromatography or chromatography on hydroxy-apatite resins. Following removal of cyclic nucleotides, the enzyme pools were dialyzed against Dialysis Buffer containing 25 mM MOPS pH 7.4, 10 µM $ZnSO_4$, 500 mM NaCl, 1 mM $CaCl_2$, 1 mM dithiothreitol, 1 mM benzamidine HCl, followed by dialysis against Dialysis buffer containing 50% glycerol. The enzyme was quick frozen with the aid of dry ice and stored at -70°C.

The resultant preparations were about >90% pure by SDS-PAGE. These preparations had specific activities of about 0.1 to 1.0 µmol cAMP hydrolyzed per minute per milligram protein.

IC_{50} Determinations

The parameter of interest in evaluating the potency of a competitive enzyme inhibitor of PDE5 and/or PDE1c and PDE6 is the inhibition constant, i.e., K_i. This parameter can be approximated by determining the IC_{50}, which is the inhibitor concentration that results in 50% enzyme inhibition, in a single dose-response experiment under the following conditions.

The concentration of inhibitor is always much greater than the concentration of enzyme, so that free inhibitor concentration (which is unknown)

is approximated by total inhibitor concentration (which is known).

A suitable range of inhibitor concentrations is chosen (i.e., inhibitor concentrations at least several fold greater and several fold less than the K_i are present in the experiment). Typically, inhibitor concentrations ranged from 10 nM to 10 μM.

The concentrations of enzyme and substrate are chosen such that less than 20% of the substrate is consumed in the absence of inhibitor (providing, e.g., maximum substrate hydrolysis of from 10 to 15%), so that enzyme activity is approximately constant throughout the assay.

The concentration of substrate is less than one-tenth the Michaelis constant (K_m). Under these conditions, the IC_{50} will closely approximate the K_i. This is because of the Cheng-Prusoff equation relating these two parameters: $IC_{50}=K_i(1+S/K_m)$, with $(1+S/K_m)$ approximately 1 at low values of S/K_m.

The IC_{50} value is estimated from the data points by fitting the data to a suitable model of the enzyme inhibitor interaction. When this interaction is known to involve simple competition of the inhibitor with the substrate, a two-parameter model can be used:

$$Y=A/(1+x/B)$$

where the y is the enzyme activity measured at an inhibitor concentration of x, A is the activity in the absence of inhibitor and B is the IC_{50}. See Y.

Cheng et al., *Biochem. Pharmacol.*, *22*:3099-3108 (1973).

Effects of inhibitors of the present invention on enzymatic activity of PDE5 and PDE6 preparations as described above were assessed in either of two assays which differed from each other principally on the basis of scale and provided essentially the same results in terms of IC_{50} values. Both assays involved modification of the procedure of Wells et al., *Biochim. Biophys. Acta*, *384*:430 (1975). The first of the assays was performed in a total volume of 200 µl containing 50 mM Tris pH 7.5, 3 mM Mg acetate, 1 mM EDTA, 50 µg/mL snake venom nucleotidase and 50 nM [^{3}H]-cGMP (Amersham). Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The assays were incubated for 30 minutes at 30°C and stopped by addition of 800 µl of 10 mM Tris pH 7.5, 10 mM EDTA, 10 mM theophylline, 0.1 mM adenosine, and 0.1 mM guanosine. The mixtures were loaded on to 0.5 mL QAE Sephadex columns, and eluted with 2 mL of 0.1 M formate (pH 7.4). The eluted radioactivity was measured by scintillation counting in Optiphase Hisafe 3.

A second, microplate, PDE assay was developed using Multiscreen plates and a vacuum manifold. The assay (100 µl) contained 50 mM Tris pH 7.5, 5 mM Mg acetate, 1 mM EDTA and 250 µg/mL snake venom nucleotidase. The other components of the reaction mixture were as described above. At the end of the incubation, the total volume of the assays were loaded on a QAE Sephadex microcolumn plate by filtration. Free radioactivity was eluted

with 200 µl of water from which 50 µl aliquots were analyzed by scintillation counting as described above.

The following examples are presented to further illustrate the preparation of the claimed invention. The scope of the present invention is not to be construed as merely consisting of the following examples.

Example 1

Compound (I) was prepared as described in U.S. patent 5,859,006 and formulated in tablets using wet granulation. Povidone was dissolved in water to make a 10% solution. The active compound, microcrystalline cellulose, croscarmellose sodium, and sodium lauryl sulfate were added to a high shear mixer and mixed for 2 minutes. The powders were wet granulated with the povidone solution and extra water as required to complete the granulation. The resultant mixture was dried in a fluid bed drier with inlet air at 70°C ± 5°C until the loss on drying was below 2.5%. The granules were passed through a Comil with a suitable screen (or a sieve) and added to a suitable mixer. The extragranular croscarmellose sodium and sodium lauryl sulfate, and the colloidal anhydrous silica were passed through a suitable sieve (e.g., 500 micron) and added to the mixer and blended 5 minutes. Magnesium stearate was added and blended for 2 minutes. The blend was compressed to a target compression/weight of 250 mg using 9 mm round normal concave tooling.

The core tablets were coated with an aqueous suspension of Opadry OY-S-7322 using an Accelacota (or similar coating pan) using inlet air at 50°C to 70°C until the tablet weight was increased by approximately 8 mg. Opadry OY-S-7322 contains methylhydroxypropylcellulose Ph.Eur., titanium dioxide Ph. Eur., Triacetin USP. Opadry increases the weight of each tablet to about 258 mg. The amount of film coat applied per tablet may be less than that stated depending on the process efficiency.

The tablets are filled into blister packs and accompanied by package insert describing the safety and efficacy of the compound.

Component	Formulations (mg per tablet)	
Selective PDE5 Inhibitor[1)]	1	5
Hydroxypropyl Methylcellulose Phthalate	1	5
Microcrystalline Cellulose	221.87	213.87
Croscarmellose Sodium	5.00	5.00
Sodium Lauryl Sulfate	2.50	2.50
Povidone K30	9.38	9.38
Purified Water, USP (water for irrigation)	q.s.	q.s.
Croscarmellose Sodium	5.00	5.00
Sodium Lauryl Sulfate	2.50	2.50
Colloidal Anhydrous Silica	0.50	0.50
Magnesium Stearate	1.25	1.25
Total core subtotal	250.00	250.00
(Film coat Opadry OY-S-7322)	about 8 mg	about 8 mg

1) Compound (I).

Example 2

The following formula is used in preparing the finished dosage form containing 10 mg of Compound (I).

Ingredient	Quantity (mg)
Granulation	
Selective PDE5 Inhibitor[1)]	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropylcellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropylcellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
	35.00
Outside Powders	
Microcrystalline Cellulose (granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
	Total 250 mg
Film coat (approximately)	11.25

Purified Water, USP is used in the manufacture of the tablets. The water is removed during processing and minimal levels remain in the finished product.

Tablets are manufactured using a wet granulation process. A step-by-step description of the process is as follows. The drug and excipients to be granulated are security sieved. The selective

PDE5 inhibitor is dry blended with lactose monohydrate (spray dried), hydroxypropylcellulose, croscarmellulose sodium, and lactose monohydrate. The resulting powder blend is granulated with an aqueous solution of hydroxypropylcellulose and sodium lauryl sulfate using a Powrex or other suitable high shear granulator. Additional water can be added to reach the desired endpoint. A mill can be used to delump the wet granulation and facilitate drying. The wet granulation is dried using either a fluid bed dryer or a drying oven. Once the material is dried, it can be sized to eliminate any large agglomerates. Microcrystalline cellulose, croscarmellose sodium, and magnesium stearate are security sieved and added to the dry sized granules. These excipients and the dry granulation are mixed until uniform using a tumble bin, ribbon mixer, or other suitable mixing equipment. The mixing process can be separated into two phases. The microcrystalline cellulose, croscarmellose sodium, and the dried granulation are added to the mixer and blended during the first phase, followed by the addition of the magnesium stearate to this granulation and a second mixing phase.

The mixed granulation then is compressed into tablets using a rotary compression machine. The core tablets are film coated with an aqueous suspension of the appropriate color mixture in a coating pan (e.g., Accela Cota). The coated tablets can be lightly dusted with talc to improve tablet handling characteristics.

The tablets are filled into plastic containers (30 tablets/container) and accompanied by

package insert describing the safety and efficacy of the compound.

Example 3

The following formula is used in preparing a finished dosage form containing 5 mg of Compound (I).

Ingredient	Quantity (mg)
Granulation	
Selective PDE5 Inhibitor[1)]	2.50
Lactose Monohydrate	79.395
Lactose Monohydrate (spray dried)	12.50
Hydroxypropylcellulose	2.00
Croscarmellose Sodium	4.50
Hydroxypropylcellulose (EF)	0.875
Sodium Lauryl Sulfate	0.35
Outside Powders	
Microcrystalline Cellulose (granular-102)	18.75
Croscarmellose Sodium	3.50
Magnesium Stearate (vegetable)	0.63
Total	**125 mg**
Film coat (approximately)	6.875

The dosage form of Example 3 was prepared in an identical manner to the dosage form of Example 2.

Example 4

Solution Capsule		
Ingredient	**mg/capsule**	**Percent (%)**
Selective PDE5 Inhibitor[1)]	10	2
PEG400 NF	490	98
Fill Weight	500	100

The gelatin capsules are precisely filled by pumping an accurate fill volume of pre-dissolved drug formulation into the partially sealed cavity of a capsule. Immediately following injection fill of the drug solution formulation, the capsule is completely heat sealed.

The capsules are filled into plastic containers and accompanied by a package insert.

Example 5

This study was a randomized, double-blind, placebo-controlled, two-way crossover design clinical pharmacology drug interaction study that evaluated the hemodynamic effects of concomitant administration of a selective PDE5 inhibitor (i.e., Compound (I)) and short-acting nitrates on healthy male volunteers. In this study, the subjects received either Compound (I) at a dose of 10 mg or a placebo, daily for seven days. On the sixth or seventh day, the subjects received sublingual nitroglycerin (0.4 mg) while supine on a tilt table. The nitroglycerin was administered 3 hours after Compound (I) dosing, and all subjects kept the nitroglycerine tablet

under their tongue until it completely dissolved. The subjects were tilted to 70° head-up every 5 minutes for a total of 30 minutes with measurement of blood pressure and heart rate. There were no discontinuations among the twenty-two healthy male subjects (ages 19 to 60 years old) that entered this study.

In a preliminary analysis of this study, Compound (I) was well tolerated and there were no serious adverse events. There were no Compound (I) changes in laboratory safety assessments or 12-lead ECGs. The most common adverse events were headache, dyspepsia, and back pain. Compound (I) demonstrated minimal, if any, effect on mean systolic blood pressure, and mean maximal nitroglycerin-induced decrease in systolic blood pressure.

Example 6

In two randomized, double-blinded placebo controlled studies, Compound (I) was administered to patients in need thereof at a range of doses, in both daily dosing and for on demand therapy, for sexual encounters and intercourse in the home setting. Doses from 5 to 20 mg of Compound (I) were efficacious and demonstrated less than 1% flushing and no reports of vision abnormalities. It was found that a 10 mg dose of Compound (I) was fully efficacious and demonstrated minimal side effects.

Enhanced erectile function was determined by the International Index of Erectile Function (IIEF) (Rosen et al., *Urology, 49*, pp. 822-830

(1997)), diaries of sexual attempts, and a global satisfaction question. Compound (I) significantly improved the percentage of successful intercourse attempts including the ability to attain and maintain an erection in both "on demand" and daily dosing regimens.

Example 7

A third clinical study was a randomized, double-blind, placebo-controlled study of Compound (I) administered "on demand" to patients with male erectile dysfunction. Compound (I) was administered over a period of eight weeks in the treatment of male erectile dysfunction (ED). Erectile dysfunction (ED) is defined as the persistent inability to attain and/or maintain an erection adequate to permit satisfactory sexual performance. "On demand" dosing is defined as intermittent administration of Compound (I) prior to expected sexual activity.

The study population consisted of 212 men, at least 18 years of age, with mild to severe erectile dysfunction. Compound (I) was orally administered as tablets of coprecipitate made in accordance with Butler U.S. Patent No. 5,985,326. Compound (I) was administered in 2 mg, 5 mg, 10 mg, and 25 mg doses, "on demand" and not more than once every 24 hours. Treatment with all nitrates, azole antifungals (e.g., ketoconazole or itraconazole), warfarin, erythromycin, or antiandrogens was not allowed at any time during the study. No other approved or experimental medications, treatments, or

devices used to treat ED were allowed. Forty-one subjects were administered a placebo.

The two primary efficacy variables were the ability of a subject to penetrate his partner and his ability to maintain an erection during intercourse, as measured by the International Index of Erectile Function (IIEF). The IIEF Questionnaire contains fifteen questions, and is a brief, reliable measure of erectile function. See R.C. Rosen et al., *Urology, 49*, pp. 822-830 (1997).

Secondary efficacy variables were IIEF domain scores for erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction; the patient's ability to achieve an erection, ability to insert his penis into his partner's vagina, completion of intercourse with ejaculation, satisfaction with the hardness of his erection, and overall satisfaction, all as measured by the Sexual Encounter Profile (SEP) diary; and a global assessment question asked at the end of the treatment period. The SEP is a patient diary instrument documenting each sexual encounter during the course of the study.

The safety aspect of the study included all enrolled subjects, and was assessed by evaluating all reported adverse events, and changes in clinical laboratory values, vital signs, physical examination results, and electrocardiogram results.

At endpoint, patients who rated their penetration ability (IIEF Question 3) as "almost always or always" were as follows: 17.5% in the placebo group, 38.1% in the 2 mg group, 48.8% in the 5 mg group, 51.2% in the 10 mg group, and 83.7% in

the 25 mg group. Comparisons revealed statistically significant differences in change in penetration ability between placebo and all dose levels of Compound (I).

At endpoint, patients who rated their ability to maintain an erection (IIEF Question 4) during intercourse as "almost always or always" are as follows: 10.0% in the placebo group, 19.5% in the 2 mg group, 32.6% in the 5 mg group, 39.0% in the 10 mg group, and 69.0% in the 25 mg group. Comparison revealed statistically significant differences in change in penetration ability between placebo and the three higher dose levels of Compound (I).

This study also included a safety evaluation. A treatment-emergent adverse event is defined as a condition not present at baseline that appeared postbaseline, or a condition present at baseline that increased in severity postbaseline. The most commonly reported treatment-emergent adverse events were headache, dyspepsia, and back pain. The incidence of treatment-emergent adverse events appeared related to dose.

Overall, this study demonstrated that all four doses of Compound (I), namely 2 mg, 5 mg, 10 mg, and 25 mg, taken "on demand" produced significant improvement, relative to placebo, in the sexual performance of men with erectile dysfunction as assessed by the IIEF, by patient diaries assessing frequency of successful intercourse and intercourse satisfaction, and by a global assessment.

The combined results from clinical studies showed that administration of Compound (I) effectively treats male erectile dysfunction, as illustrated in the following table.

IIEF ERECTILE FUNCTION DOMAIN (Change from Baseline)			
Unit Dose of Compound (I)	**n**	**Mean ± SD**	**p**
placebo	131	0.8 ± 5.3	
2 mg	75	3.9 ± 6.1	<.001
5 mg	79	6.6 ± 7.1	<.001
10 mg	135	7.9 ± 6.7	<.001
25 mg	132	9.4 ± 7.0	<.001
50 mg	52	9.8 ± 5.5	<.001
100 mg	49	8.4 ± 6.1	<.001

n is number of subjects, SD is standard deviation.

However, it also was observed from the combined clinical studies that the percent of treatment-emergent adverse events increased with an increasing unit dose of Compound (I), as illustrated in the following table:

Treatment-Emergent Adverse Events (%)							
	Unit Dose of Compound (I) (mg)						
Event	Placebo	2	5	10	25	50	100
Headache	10	12	10	23	29	34	46
Dyspepsia	6	3	14	13	19	20	25
Back Pain	5	3	3	15	18	24	22
Myalgia	3	0	3	9	16	20	29
Rhinitis	3	7	3	4	4	0	2
Conjunctivitis	1	0	1	1	0	2	5
Eyelid Edema	0	0	0	1	1	2	3
Flushing	0	0	0	<1	0	3	7
Vision Abnormalities	0	0	0	0	0	0	0

The above table shows an increase in adverse events at 25 mg through 100 mg unit doses. Accordingly, even though efficacy in the treatment of ED was observed at 25 mg to 100 mg doses, the adverse events observed from 25 mg to 100 mg doses must be considered.

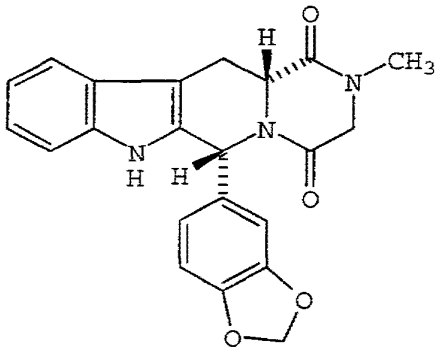
In accordance with the present invention, a unit dose of about 1 to about 20 mg, preferably about 2 to about 20 mg, more preferably about 5 to about 20 mg, and most preferably about 5 to about 15 mg, of Compound (I), administered up to a maximum of 20 mg per 24-hour period, both effectively treats ED and minimizes or eliminates the occurrence of adverse side effects. Importantly, no vision abnormalities were reported and flushing was essentially eliminated. Surprisingly, in addition to treating ED, with at about 1 to about 20 mg unit dose Compound (I), with a minimum of adverse side effects, individuals undergoing nitrate therapy also can be

treated for ED by the method and composition of the present invention.

The principles, preferred embodiments, and modes of operation of the present invention have been described in the foregoing specification. The invention intended to be protected herein, however, is not construed to be limited to the particular forms disclosed, because they are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention.

WHAT IS CLAIMED IS:

1. A pharmaceutical unit dosage composition comprising about 1 to about 20 mg of a compound having the structural formula:



said unit dosage form suitable for oral administration.

2. The dosage form of claim 1 comprising about 2 to about 20 mg of the compound in unit dosage form.

3. The dosage form of claim 1 comprising about 5 to about 20 mg of the compound in unit dosage form.

4. The dosage form of claim 2 comprising about 2.5 mg of the compound in unit dosage form.

5. The dosage form of claim 3 comprising about 5 mg of the compound in unit dosage form.

6. The dosage form of claim 3 comprising about 10 mg of the compound in unit dosage form.

7. The dosage form of claims 1 through 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

8. The dosage form of claims 1 through 6 wherein the unit dose is in the form of a tablet.

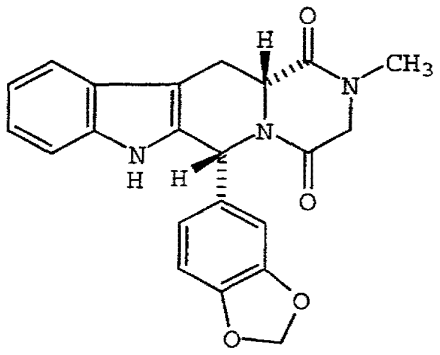
9. The dosage form of claims 1 through 6 for use in treating a condition where inhibition of PDE5 is desirable.

10. The dosage form of claim 9 wherein the condition is a sexual dysfunction.

11. The dosage form of claim 10 wherein the sexual dysfunction is male erectile dysfunction.

12. The dosage form of claim 10 wherein the sexual dysfunction is female arousal disorder.

13. A method of treating sexual dysfunction in a patient in need thereof comprising administering one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day, of a compound having the structure



14. The method of claim 13 wherein the unit dose contains about 2 to about 20 mg of the compound.

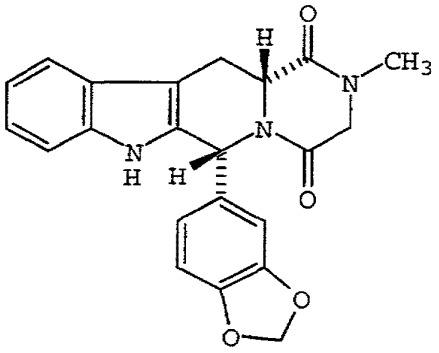
15. The method of claim 13 wherein the unit dose contains about 5 mg of the compound.

16. The method of claim 13 wherein the unit dose contains about 10 mg of the compound and is administered once per day.

17. The method of claim 13 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

18. The invention as hereinbefore described.

19. Use of a unit dose containing about 1 to about 20 mg of a compound having the structure



for the manufacture of a medicament for the treatment of sexual dysfunction in a patient in need thereof.

DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "**UNIT DOSAGE FORM**," the specification of which (check one): ☐ is attached hereto; ☐ was filed on _____ _____ as Application Serial No. _____ and was amended on _____ (if applicable); ☒ was filed as PCT International Application No. PCT/US00/11129 on April 26, 2000, and was amended under Article 19 on _____ (if applicable). I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

			Priority Claimed	
PCT/US00/11129	PCT	26/04/00	☒	☐
(Application Serial Number)	(Country)	(Day/Month/Year Filed)	Yes	No
			☐	☐
(Application Serial Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

60/132,036	30/04/99
(Application Serial Number)	(Day/Month/Year Filed)
(Application Serial Number)	(Day/Month/Year Filed)

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or PCT international application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(Application Serial Number)	(Day/Month/Year Filed)	(Status-Patented, Pending or Abandoned)
(Application Serial Number)	(Day/Month/Year Filed)	(Status-Patented, Pending or Abandoned)

I hereby 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 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: I hereby appoint as my attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

John B. Lungmus(18,566)	Richard H. Anderson (26,526)	Martin J. Hirsch (32,237)	James A. Flight (37,622)
Allen H. Gerstein (22,218)	Patrick D. Ertel (26,877)	James J. Napoli (32,361)	Roger A. Heppermann (37,641)
Nate F. Scarpelli (22,320)	Richard B. Hoffman(26,910)	Richard M. La Barge (32,254)	David A. Gass (38,153)
Michael F. Borun (25,447)	James P. Zeller (28,491)	Douglass C. Hochstetler (33,710)	Gregory C. Mayer (38,238)
Trevor B. Joike (25,542)	Kevin D. Hogg (31,839)	Robert M. Gerstein (34,824)	Michael R. Weiner (38,359)
Carl E. Moore, Jr. (26,487)	Jeffrey S. Sharp (31,879)	Anthony G. Sitko (36,278)	William K. Merkel (40,725)

Send correspondence to: James J. Napoli

FIRM NAME	PHONE NO.	STREET	CITY & STATE	ZIP CODE
Marshall, Gerstein & Borun	312-474-6300	6300 Sears Tower 233 South Wacker Drive	Chicago, Illinois	60606-6402

Full Name of First or Sole Inventor	Citizenship
William Ernest Pullman	~~United States of America~~ AUSTRALIA
Residence Address - Street 42 Annin Road	Post Office Address - Street 42 Annin Road
City (Zip) Far Hills (07931) NJ	City (Zip) Far Hills (07931)
State or Country New Jersey	State or Country New Jersey
Date ☒ 11/10/01	Signature ☒

Second Joint Inventor, if any	Citizenship
John Steven Whitaker	United States of America
Residence Address - Street 19340 162nd Avenue	Post Office Address - Street 19342 162nd Avenue
City (Zip) Woodinville (98072)	City (Zip) Woodinville (98072)
State or Country Washington	State or Country Washington
Date ☒	Signature ☒

Third Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Fourth Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

(2) Over

APPLICABLE RULES AND STATUTES

37 CFR 1.56. DUTY OF DISCLOSURE - INFORMATION MATERIAL TO PATENTABILITY (Applicable Portion)

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and
(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentability defines, to make sure that any material information contained therein is disclosed to the Office.

Information relating to the following factual situations enumerated in 35 USC 102 and 103 may be considered material under 37 CFR 1.56(a).

35 U.S.C. 102. CONDITIONS FOR PATENTABILITY: NOVELTY AND LOSS OF RIGHT TO PATENT

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or

(f) he did not himself invent the subject matter sought to be patented, or

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C. 103. CONDITIONS FOR PATENTABILITY; NON-OBVIOUS SUBJECT MATTER (Applicable Portion)

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35 U.S.C. 112. SPECIFICATION (Applicable Portion)

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

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PCT/US00/11129	PCT	26/04/00	☒	☐
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Marshall, Gerstein & Borun	312-474-6300	6300 Sears Tower 233 South Wacker Drive	Chicago, Illinois	60606-6402

Full Name of First or Sole Inventor William Ernest Pullman	Citizenship United States of America
Residence Address - Street 3004 Towne Drive	Post Office Address - Street 3004 Towne Drive
City (Zip) Carmel (46032)	City (Zip) Carmel (46032)
State or Country Indiana	State or Country Indiana
Date ☒	Signature ☒

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City (Zip) Woodinville (98072) WA	City (Zip) Woodinville (98072)
State or Country Washington	State or Country Washington
Date ☒ 11 Octbr 2001	Signature ☒

Third Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Fourth Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

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(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10/031556

FILED UNDER 35 U.S.C.371

PATENT NUMBER and ISSUE DATE

U.S. **UTILITY** Patent Application

APPL NUM	FILING DATE	CLASS	SUBCLASS	GAU	EXAMINER
10031556	10/19/2001	514	249	1614	

**APPLICANTS: Pullman William; Whitaker John;

**CONTINUING DATA VERIFIED:
THIS APPLICATION IS A 371 OF PCT/US00/11129 04/26/2000
AND CLAIMS BENEFIT OF 60/132,036 04/30/1999

** FOREIGN APPLICATIONS VERIFIED:

PG-PUB DO NOT PUBLISH ☐ RESCIND ☐

Foreign priority claimed ☐ yes ☐ no
35 USC 119 conditions met ☐ yes ☐ no
Verified and Acknowledged Examiner's initials

ATTORNEY DOCKET NO
29342/36206A

TITLE : Compositions comprising phosphodiesterase inhabitors for the treatment of sexual disfunction

U.S.DEPT. OF COMM./PAT.& TM-PTO-436L(Rev. 12-94)

NOTICE OF ALLOWANCE MAILED		Assistant Examiner	CLAIMS ALLOWED	
			Total Claims	Print Claim for O.G
ISSUE FEE			DRAWING	
Amount Due	Date Paid		Sheets Drwg. / Figs.Drwg. / Print Fig.	
☐ TERMINAL DISCLAIMER		Primary Examiner		
		PREPARED FOR ISSUE	Application Examiner	

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368, Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

FILED WITH: ☐ DISK (CRF) ☐ CD-ROM
(Attached in pocket on right inside flap)

BEST AVAILABLE COPY

SEARCH

Class	Sub.	Date	Exmr.
514	25J	8/28/02	[illegible]
updated		4/9/03	[illegible]
updated		9/16/03	[illegible]

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

	Date	Exmr.
Palm Expo Inventor search. OSP	8/28/02	[illegible]
STN: Registry, CAPLUS, Embase, WPIDS, Biosis, Medline see search inside	7/15/02	[illegible]

ISSUE SLIP STAPLE AREA (for additional cross-references)

ISSUING CLASSIFICATION			
ORIGINAL		CROSS REFERENCE(S)	
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)
INTERNATIONAL CLASSIFICATION			
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INDEX OF CLAIMS

✓ ..... Rejected - (Through numeral) ... Canceled N ..... Non-elected A ..... Appeal
= ..... Allowed + ... Restricted I ..... Interference O ..... Objected

Claim Final	Claim Original	Date											
	1	✓	4/29/02	✓	7/10/02	9/16/03							
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If more than 150 claims or 9 actions staple additional sheet here

IC10 [redacted] c'd PCT/PTO 19 OCT 2001

FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPART[redacted] F COMMERCE PATENT AND TRADEMARK OFFICE

ATTO[redacted]'S DOCKET NUMBER
29342/36206A

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
10/031556

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/11129	26 April 2000	30 April 1999

TITLE OF INVENTION
UNIT DOSAGE FORM

APPLICANT(S) FOR DO/EO/US
PULLMAN, William Ernest and WHITAKER, John Steven

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Return receipt postcard

PCTUS1/REV03

531 Rec'd PCT/PTO 19 OCT 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/031506	PCT/US00/11129	29342/36206A

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	17 - 20 =	0	x $18.00	**$0.00**	
Independent claims	2 - 3 =	0	x $84.00	**$0.00**	
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$890.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**	
SUBTOTAL =				**$890.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
TOTAL NATIONAL FEE =				**$890.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
TOTAL FEES ENCLOSED =				**$890.00**	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$890.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **13-2855** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

NAPOLI, James J.
Customer No. 04743
Marshall, Gerstein & Borun
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
United States of America

SIGNATURE

James J. Napoli
NAME

32,361
REGISTRATION NUMBER

19 October 2001
DATE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	)
WILLIAM E. PULLMAN ET AL.	)
U.S. National Phase of PCT/US00/11129 filed April 26, 2000	)
Filed: Herewith	)
For: **UNIT DOSAGE FORM**	)
Group Art Unit: Unassigned	)
Examiner: Unassigned	)
Attorney Docket No. 29342/36206A	)

CERTIFICATION UNDER 37 CFR 1.10

Box PCT
Commissioner for Patents
Washington, D.C. 20231

I hereby certify the attached items are being deposited with the United States Postal Service on October 19, 2001 in an envelope addressed to Box PCT, Commissioner for Patents, Washington, D.C. 20231 utilizing the "Express Mail Post Office to Addressee" service of the United States Postal Service under Mailing No. EK 657817671US:

a. Transmittal letter to the United States Designated/Elected Office (DO/EO/US) concerning a filing under 35 U.S.C. 371;

b. Copies of Form PCT/ISA/210 and Form PCT/IPEA/409;

c. Preliminary Amendment dated 19 October 2001;

d. Declaration and Power of Attorney for William Ernest PULLMAN;

e. Declaration and Power of Attorney for John Steven WHITAKER;

f. A check in the amount of $890.00.

Richard Zimmermann

Date: October 19, 2001

UNIT DOSAGE FORM

CROSS REFERENCE TO RELATED APPLICATIONS

SUB A1

This application claims the benefit of provisional patent application Serial No. 60/132,036, filed April 30, 1999.

FIELD OF THE INVENTION

The present invention relates to a highly selective phosphodiesterase (PDE) enzyme inhibitor and to its use in a pharmaceutical unit dosage form. In particular, the present invention relates to a potent inhibitor of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase type 5 (PDE5) that when incorporated into a pharmaceutical product is useful for the treatment of sexual dysfunction. The unit dosage form described herein is characterized by selective PDE5 inhibition, and accordingly, provides a benefit in therapeutic areas where inhibition of PDE5 is desired, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes.

BACKGROUND OF THE INVENTION

The biochemical, physiological, and clinical effects of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE) inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or

endocrine function is desired. Type 5 cGMP-specific phosphodiesterase (PDE5) is the major cGMP hydrolyzing enzyme in vascular smooth muscle, and its expression in penile corpus cavernosum has been reported (Taher et al., *J. Urol., 149*, p. 285A (1993)). Thus, PDE5 is an attractive target in the treatment of sexual dysfunction (Murray, *DN&P 6(3)*, pp. 150-56 (1993)).

A pharmaceutical product, which provides a PDE5 inhibitor, is currently available and marketed under the trademark VIAGRA®. The active ingredient in VIAGRA® is sildenafil. The product is sold as an article of manufacture including 25, 50, and 100 mg tablets of sildenafil and a package insert. The package insert provides that sildenafil is a more potent inhibitor of PDE5 than other known phosphodiesterases (greater than 80 fold for PDE1 inhibition, greater than 1,000 fold for PDE2, PDE3, and PDE4 inhibition). The IC_{50} for sildenafil against PDE5 has been reported as 3 nM (*Drugs of the Future, 22(2)*, pp. 138-143 (1997)) and as 3.9 nM (Boolel et al., *Int. J. of Impotence, 8*, pp. 47-52 (1996)). Sildenafil is described as having a 4,000-fold selectivity for PDE5 versus PDE3, and only a 10-fold selectivity for PDE5 versus PDE6. Its relative lack of selectivity for PDE6 is theorized to be the basis for abnormalities related to color vision.

While sildenafil has obtained significant commercial success, it has fallen short due to its significant adverse side effects, including facial flushing (10% incidence rate). Adverse side effects limit the use of sildenafil in patients suffering from vison abnormalities, hypertension, and, most

significantly, by individuals who use organic nitrates (Welds et al., *Amer. J. of Cardiology, 83(5A)*, pp. 21(C)-28(C) (1999)).

The use of sildenafil in patients taking organic nitrates causes a clinically significant drop in blood pressure which could place the patient in danger. Accordingly, the package label for sildenafil provides strict contraindications against its use in combination with organic nitrates (e.g., nitroglycerin, isosorbide mononitrate, isosorbide nitrate, erythrityl tetranitrate) and other nitric oxide donors in any form, either regularly or intermittently, because sildenafil potentiates the hypotensive effects of nitrates. See C.R. Conti et al., *Amer. J. of Cardiology, 83(5A)*, pp. 29C-34C (1999). Thus, even with the availability of sildenafil, there remains a need to identify improved pharmaceutical products that are useful in treating sexual dysfunction.

Daugan U.S. Patent 5,859,006 discloses certain tetracyclic derivatives that are potent inhibitors of cGMP-specific PDE, or PDE5. The IC_{50} of the compounds disclosed in U.S. Patent No. 5,859,006 is reported in the range of 1 nM to 10 µM. The oral dosage for such compounds is 0.58 mg daily for an average adult patient (70 kg). Thus, unit dosage forms (tablets or capsules) are reported as 0.2 to 400 mg of active compound. Significant adverse side effects attributed to compounds disclosed in U.S. Patent No. 5,859,006 are not disclosed.

Applicants have discovered that one such tetracyclic derivative, (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, alternatively named (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, and referred to herein as Compound (I), can be administered in a unit dose that provides an effective treatment without the side effects associated with the presently marketed PDE5 inhibitor, sildenafil. Prior to the present invention such side effects were considered inherent to the inhibition of PDE5.

Significantly, applicants' clinical studies also reveal that an effective product having a reduced tendency to cause flushing in susceptible individuals can be provided. Most unexpectedly, the product also can be administered with clinically insignificant side effects associated with the combined effects of a PDE5 inhibitor and an organic nitrate. Thus, the contraindication once believed necessary for a product containing a PDE5 inhibitor is unnecessary when Compound (I) is administered as a unit dose of about 1 to about 20 mg, as disclosed herein. Thus, the present invention provides an effective therapy for sexual dysfunction in individuals who previously were untreatable or suffered from unacceptable side effects, including individuals having cardiovascular disease, such as in individuals requiring nitrate therapy, having suffered a myocardial infarction more than three months before the onset of sexual dysfunction therapy, and suffering from class 1 congestive heart failure, or individuals suffering from vision abnormalities.

The present invention provides Compound (I) in a unit dosage form. That is, the present invention provides a pharmaceutical unit dosage form suitable for oral administration comprising about 1 to about 20 mg Compound (I).

SUMMARY OF THE INVENTION

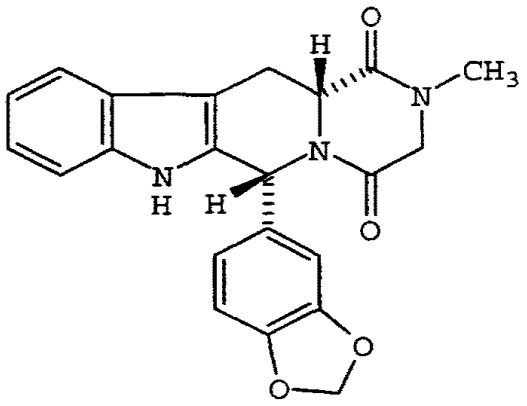
The present invention provides a pharmaceutical dosage form for human pharmaceutical use, comprising about 1 to about 20 mg of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione in a unit dosage form suitable for oral administration.

The present invention further provides a method of treating conditions where inhibition of PDE5 is desired, which comprises administering to a patient in need thereof an oral dosage form containing about 1 to about 20 mg of a selective PDE5 inhibitor, as needed, up to a total dose of 20 mg per day. The invention further provides the use of an oral dosage form comprising a selective PDE5 inhibitor at a dosage of about 1 to about 20 mg for the treatment of sexual dysfunction.

Specific conditions that can be treated by the present invention, include, but are not limited to, male erectile dysfunction and female sexual dysfunction, particularly female arousal disorder, also known as female sexual arousal disorder.

In particular, the present invention is directed to a pharmaceutical unit dosage composition

comprising about 1 to about 20 mg of a compound having the structural formula:



said unit dosage form suitable for oral administration, and method of treating sexual dysfunction using the pharmaceutical unit dose composition.

DETAILED DESCRIPTION

For purposes of the present invention as disclosed and described herein, the following terms and abbreviations are defined as follows.

The term "container" means any receptacle and closure therefor suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

The term "IC_{50}" is the measure of potency of a compound to inhibit a particular PDE enzyme (e.g., PDE1c, PDE5, or PDE6). The IC_{50} is the concentration of a compound that results in 50% enzyme inhibition in a single dose-response experiment. Determining the IC_{50} value for a compound is readily

carried out by a known *in vitro* methodology generally described in Y. Cheng et al., *Biochem. Pharmacol., 22*, pp. 3099-3108 (1973).

The term "package insert" means information accompanying the product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

The term "oral dosage form" is used in a general sense to reference pharmaceutical products administered orally. Oral dosage forms are recognized by those skilled in the art to include such forms as liquid formulations, tablets, capsules, and gelcaps.

The term "vision abnormalities" means abnormal vision characterized by blue-green vision believed to be caused by PDE6 inhibition.

The term "flushing" means an episodic redness of the face and neck attributed to vasodilation caused by ingestion of a drug, usually accompanied by a feeling of warmth over the face and neck and sometimes accompanied by perspiration.

The term "free drug" means solid particles of drug not intimately embedded in a polymeric coprecipitate.

The presently claimed dosage form preferably is packaged as an article of manufacture for human pharmaceutical use, comprising a package insert, a container, and a dosage form comprising about 1 to about 20 mg of Compound (I)

The package insert provides a description of how to administer a pharmaceutical product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding the use of the product. The package insert generally is regarded as the label of the pharmaceutical product. The package insert incorporated into the article of manufacture indicates that Compound (I) is useful in the treatment of conditions wherein inhibition of PDE5 is desired. The package insert also provides instructions to administer one or more about 1 to about 20 mg unit dosage forms as needed, up to a maximum total dose of 20 mg per day. Preferably, the dose administered is about 5 to about 20 mg/day, more preferably about 5 to about 15 mg/day. Most preferably, a 10 mg dosage form is administered once per day.

Preferred conditions to be treated include sexual dysfunction (including male erectile dysfunction; and female sexual dysfunction, and more preferably female arousal disorder (FAD)). The preferred condition to be treated is male erectile dysfunction.

Significantly, the package insert supports the use of the product to treat sexual dysfunction in patients suffering from a retinal disease, for example, diabetic retinopathy or retinitis pigmentosa, or in patients who are using organic nitrates. Thus, the package insert preferably is free of contraindications associated with these conditions, and particularly the administration of the dosage form with an organic nitrate. More

preferably, the package insert also is free of any cautions or warnings both associated with retinal diseases, particularly retinitis pigmentosa, and associated with individuals prone to vision abnormalities. Preferably, the package insert also reports incidences of flushing below 2%, preferably below 1%, and most preferably below 0.5%, of the patients administered the dosage form. The incidence rate of flushing demonstrates marked improvement over prior pharmaceutical products containing a PDE5 inhibitor.

The container used in the article of manufacture is conventional in the pharmaceutical arts. Generally, the container is a blister pack, foil packet, glass or plastic bottle and accompanying cap or closure, or other such article suitable for use by the patient or pharmacist. Preferably, the container is sized to accommodate 1-1000 solid dosage forms, preferably 1 to 500 solid dosage forms, and most preferably, 5 to 30 solid dosage forms.

Oral dosage forms are recognized by those skilled in the art to include, for example, such forms as liquid formulations, tablets, capsules, and gelcaps. Preferably the dosage forms are solid dosage forms, particularly, tablets comprising about 1 to about 20 mg of Compound (I). Any pharmaceutically acceptable excipients for oral use are suitable for preparation of such dosage forms. Suitable pharmaceutical dosage forms include coprecipitate forms described, for example, in Butler U.S. Patent No. 5,985,326, incorporated herein by reference. In preferred embodiments, the unit dosage form of the

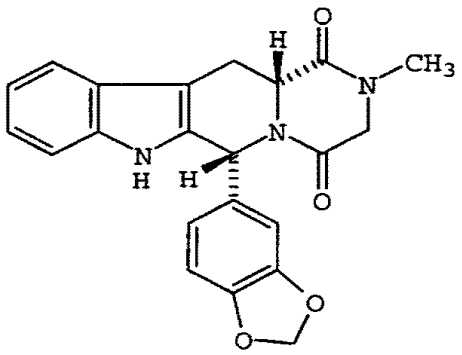
present invention is a solid free of a coprecipitate form of Compound (I), but rather contains solid Compound (I) as a free drug.

Preferably, the tablets comprise pharmaceutical excipients generally recognized as safe such as lactose, microcrystalline cellulose, starch, calcium carbonate, magnesium stearate, stearic acid, talc, and colloidal silicon dioxide, and are prepared by standard pharmaceutical manufacturing techniques as described in *Remington's Pharmaceutical Sciences, 18th Ed.*, Mack Publishing Co., Easton, PA (1990). Such techniques include, for example, wet granulation followed by drying, milling, and compression into tablets with or without film coating; dry granulation followed by milling, compression into tablets with or without film coating; dry blending followed by compression into tablets, with or without film coating; molded tablets; wet granulation, dried and filled into gelatin capsules; dry blend filled into gelatin capsules; or suspension and solution filled into gelatin capsules. Generally, the solid dosage forms have identifying marks which are debossed or imprinted on the surface.

The present invention is based on detailed experiments and clinical trials, and the unexpected observations that side effects previously believed to be indicative of PDE5 inhibition can be reduced to clinically insignificant levels by the selection of a compound and unit dose. This unexpected observation enabled the development of a unit dosage form that incorporates Compound (I) in about 1 to about 20 mg per unit dosage forms that, when orally administered, minimizes undesirable side effects previ-

ously believed unavoidable. These side effects include facial flushing, vision abnormalities, and a significant decrease in blood pressure, when Compound (I) is administered alone or in combination with an organic nitrate. The minimal effect of Compound (I), administered in about 1 to about 20 mg unit dosage forms, on PDE6 also allows the administration of a selective PDE5 inhibitor to patients suffering from a retinal disease, like diabetic retinopathy or retinitis pigmentosa.

Compound (I) has the following structural formula:



(I)

The compound of structural formula (I) was demonstrated in human clinical studies to exert a minimal impact on systolic blood pressure when administered in conjunction with organic nitrates. By contrast, sildenafil demonstrates a four-fold greater decrease in systolic blood pressure over a placebo, which leads to the contraindications in the VIAGRA® insert, and in warnings to certain patients.

The following illustrates the PDE5 and PDE6 IC_{50} values for the compound of structural

formula (I) determined by the procedures described herein.

Compound	PDE5 IC_{50} (nM)	PDE6 IC_{50} (nM)	PDE6/PDE5
I	2.5	3400	1360

The compound of structural formula (I) additionally demonstrates an IC_{50} against PDE1c of 10,000, and a ratio of PDE1c/PDE5 of 4,000.

PREPARATIONS

Human PDE5 Preparation

Recombinant production of human PDE5 was carried out essentially as described in Example 7 of U.S. Patent No. 5,702,936, incorporated herein by reference, except that the yeast transformation vector employed, which is derived from the basic ADH2 plasmid described in V. Price et al., *Methods in Enzymology*, 1985, pages 308-318 (1990), incorporated yeast ADH2 promoter and terminator sequences rather than ADH1 promoter and terminator sequences and the *Saccharomyces cerevisiase* host was the protease-deficient strain BJ2-54 deposited on August 31, 1998 with the American Type Culture Collection, Manassas, Virginia, under accession number ATCC 74465. Transformed host cells were grown in 2X SC-leu medium, pH 6.2, with trace metals, and vitamins. After 24 hours, YEP medium containing glycerol was added to a final concentration of 2X YEP/3% glycerol. Approximately 24 hours later, cells were harvested, washed, and stored at -70°C.

Cell pellets (29 g) were thawed on ice with an equal volume of lysis buffer (25 mM Tris-Cl, pH 8, 5 mM $MgCl_2$, 0.25 mM dithiothreitol, 1 mM benzamidine, and 10 µM $ZnSO_4$). Cells were lysed in a microfluidizer with N_2 at 20,000 psi. The lysate was centrifuged and filtered through 0.45 µm disposable filters. The filtrate was applied to a 150 mL column of Q Sepharose Fast Flow (Pharmacia). The column was washed with 1.5 volumes of Buffer A (20 mM Bis-Tris Propane, pH 6.8, 1 mM $MgCl_2$, 0.25 mM dithiothreitol, 10 µM $ZnSO_4$) and eluted with a step gradient of 125 mM NaCl in Buffer A followed by a linear gradient of 125-1000 mM NaCl in Buffer A.

Active fractions from the linear gradient were applied to a 180 mL ceramic hydroxyapatite column in Buffer B (20 mM Bis-Tris Propane (pH 6.8), 1 mM $MgCl_2$, 0.25 mM dithiothreitol, 10 µM $ZnSO_4$, and 250 mM KCl). After loading, the column was washed with 2 volumes of Buffer B and eluted with a linear gradient of 0-125 mM potassium phosphate in Buffer B. Active fractions were pooled, precipitated with 60% ammonium sulfate, and resuspended in Buffer C (20 mM Bis-Tris Propane, pH 6.8, 125 mM NaCl, 0.5 mM dithiothreitol, and 10 µM $ZnSO_4$). The pool was applied to a 140 mL column of Sephacryl S-300 HR and eluted with Buffer C. Active fractions were diluted to 50% glycerol and stored at -20°C. The resultant preparations were about 85% pure by SDS-PAGE.

Assay for PDE Activity

Activity of PDE5 can be measured by standard assays in the art. For example, specific

activity of any PDE can be determined as follows. PDE assays utilizing a charcoal separation technique were performed essentially as described in Loughney et al., (1996), *The Journal of Biological Chemistry, 271*:796-806. In this assay, PDE5 activity converts [^{32}P]cGMP to [^{32}P]5'GMP in proportion to the amount of PDE5 activity present. The [^{32}P]5'GMP then is quantitatively converted to free [^{32}P] phosphate and unlabeled adenosine by the action of snake venom 5'-nucleotidase. Hence, the amount of [^{32}P] phosphate liberated is proportional to enzyme activity. The assay is performed at 30 C in a 100 µL reaction mixture containing (final concentrations) 40 mM Tris-Cl (pH 8.0), 1 µM $ZnSO_4$, 5 mM $MgCl_2$, and 0.1 mg/mL bovine serium albumin. PDE5 is present in quantities that yield <30% total hydrolysis of substrate (linear assay conditions). The assay is initiated by addition of substrate (1 mM [^{32}P]cGMP), and the mixture is incubated for 12 minutes. Seventy-five (75) µg of *Crotalus atrox* venom then is added, and the incubation is continued for 3 more minutes (15 minutes total). The reaction is stopped by addition of 200 mL of activated charcoal (25 mg/-mL suspension in 0.1 M NaH_2PO_4, pH 4). After centrifugation (750 x g for 3 minutes) to sediment the charcoal, a sample of the supernatant is taken for radioactivity determination in a scintillation counter and the PDE5 activity is calculated. The preparations had specific activities of about 3 µmoles cGMP hydrolyzed per minute per milligram protein.

Bovine PDE6 Preparation

Bovine PDE6 was supplied by Dr. N. Virmaux, INSERM U338, Strasbourg. Bovine retinas were prepared as described by Virmaux et al., *FEBS Letters, 12(6)*, pp. 325-328 (1971) and see also, A. Sitaramayya et al., *Exp. Eye Res., 25*, pp. 163-169 (1977). Briefly, unless stated otherwise, all operations were done in the cold and in dim red light. Eyes were kept in the cold and in the dark for up to four hours after slaughtering.

Preparation of bovine retinal outer segment (ROS) basically followed procedures described by Schichi et al., *J. Biol. Chem., 224*:529 (1969). In a typical experiment, 35 bovine retinas were ground in a mortar with 35 mL 0.066 M phosphate buffer, pH 7.0, made up to 40% with sucrose, followed by homogenization in a Potter homogenizer (20 up and down strokes). The suspension was centrifuged at 25,000 x g for 20 minutes. The pellet was homogenized in 7.5 mL 0.006 M phosphate buffer (40% in sucrose), and carefully layered under 7.5 mL of phosphate buffer (containing no sucrose). Centrifugation was conducted in a swing-out rotor at 45,000 x g for 20 minutes, and produced a pellet which is black at the bottom, and also a red band at the interface 0.066 M. phosphate--40% sucrose/0.066 M phosphate (crude ROS). The red material at the interface was removed, diluted with phosphate buffer, spun down to a pellet, and redistributed in buffered 40% sucrose as described above. This procedure was repeated 2 or 3 times until no pellet was formed. The purified ROS was washed in phosphate

buffer and finally spun down to a pellet at 25,000 x g for 20 minutes. All materials were then kept frozen until used.

Hypotonic extracts were prepared by suspending isolated ROS in 10 mM Tris-Cl pH 7.5, 1 mM EDTA, and 1 mM dithioerythritol, followed by centrifugation at 100,000 x g for 30 minutes.

The preparation was reported to have a specific activity of about 35 nmoles cGMP hydrolyzed per minute per milligram protein.

PDE1c Preparation from *Spodoptera fugiperda* Cells (Sf9)

Cell pellets (5g) were thawed on ice with 20ml of Lysis Buffer (50mM MOPS pH 7.4, 10µM $ZnSO_4$, 0.1mM $CaCl_2$, 1mM DTT, 2mM benzamidine HCl, 5µg/ml each of pepstatin, leupeptin, and aprotenin). Cells were lysed by passage through a French pressure cell (SLM-Aminco) while temperatures were maintained below 10°C. The resultant cell homogenate was centrifuged at 36,000 rpm at 4°C for 45 minutes in a Beckman ultracentrifuge using a Type TI45 rotor. The supernatant was discarded and the resultant pellet was resuspended with 40 ml of Solubilization Buffer (Lysis Buffer containing 1M NaCl, 0.1M $MgCl_2$, 1mM $CaCl_2$, 20µg/ml calmodulin, and 1% Sulfobetaine SB12 (Z3-12) by sonicating using a VibraCell tuner with a microtip for 3 x 30 seconds. This was performed in a crushed ice/salt mix for cooling. Following sonication, the mixture was slowly mixed for 30 minutes at 4°C to finish solubilizing membrane bound proteins. This mixture was centrifuged

in a Beckman ultracentrifuge using a type TI45 rotor at 36,000 rpm for 45 minutes. The supernatant was diluted with Lysis Buffer containing 10µg/ml calpain inhibitor I and II. The precipitated protein was centrifuged for 20 minutes at 9,000 rpm in a Beckman JA-10 rotor. The recovered supernatant then was subjected to Mimetic Blue AP Agarose Chromatography.

In order to run the Mimetic Blue AP Agarose Column, the resin initially was shielded by the application of 10 bed volumes of 1% polyvinyl-pyrrolidine (i.e., MW of 40,000) to block nonspecific binding sites. The loosely bound PVP-40 was removed by washing with 10 bed volumes of 2M NaCl, and 10 mM sodium citrate pH 3.4. Just prior to addition of the solubilized PDE1c3 sample, the column was equilibrated with 5 bed volumes of Column Buffer A (50 mM MOPS pH 7.4, 10µM $ZnSO_4$, 5mM $MgCl_2$, 0.1 mM $CaCl_2$, 1 mM DTT, 2 mM benzamidine HCl).

The solubilized sample was applied to the column at a flow rate of 2 ml/min with recycling such that the total sample was applied 4 to 5 times in 12 hours. After loading was completed, the column was washed with 10 column volumes of Column Buffer A, followed by 5 column volumes of Column Buffer B (Column Buffer A containing 20 mM 5'-AMP), and followed by 5 column volumes of Column Buffer C (50 mM MOPS pH 7.4, 10 µM $ZnSO_4$, 0.1 mM $CaCl_2$, 1 mM dithiothreitol, and 2 mM benzamidine HCl). The enzyme was eluted into three successive pools. The first pool consisted of enzyme from a 5 bed volume wash with Column Buffer C containing 1 mM cAMP. The second pool consisted of enzyme from a 10 bed volume wash with Column Buffer C containing 1 M NaCl. The

final pool of enzyme consisted of a 5 bed volume wash with Column Buffer C containing 1 M NaCl and 20 mM cAMP.

The active pools of enzyme were collected and the cyclic nucleotide removed via conventional gel filtration chromatography or chromatography on hydroxy-apatite resins. Following removal of cyclic nucleotides, the enzyme pools were dialyzed against Dialysis Buffer containing 25 mM MOPS pH 7.4, 10 µM $ZnSO_4$, 500 mM NaCl, 1 mM $CaCl_2$, 1 mM dithiothreitol, 1 mM benzamidine HCl, followed by dialysis against Dialysis buffer containing 50% glycerol. The enzyme was quick frozen with the aid of dry ice and stored at -70°C.

The resultant preparations were about >90% pure by SDS-PAGE. These preparations had specific activities of about 0.1 to 1.0 µmol cAMP hydrolyzed per minute per milligram protein.

IC_{50} Determinations

The parameter of interest in evaluating the potency of a competitive enzyme inhibitor of PDE5 and/or PDE1c and PDE6 is the inhibition constant, i.e., K_i. This parameter can be approximated by determining the IC_{50}, which is the inhibitor concentration that results in 50% enzyme inhibition, in a single dose-response experiment under the following conditions.

The concentration of inhibitor is always much greater than the concentration of enzyme, so that free inhibitor concentration (which is unknown)

is approximated by total inhibitor concentration (which is known).

A suitable range of inhibitor concentrations is chosen (i.e., inhibitor concentrations at least several fold greater and several fold less than the K_i are present in the experiment). Typically, inhibitor concentrations ranged from 10 nM to 10 μM.

The concentrations of enzyme and substrate are chosen such that less than 20% of the substrate is consumed in the absence of inhibitor (providing, e.g., maximum substrate hydrolysis of from 10 to 15%), so that enzyme activity is approximately constant throughout the assay.

The concentration of substrate is less than one-tenth the Michaelis constant (K_m). Under these conditions, the IC_{50} will closely approximate the K_i. This is because of the Cheng-Prusoff equation relating these two parameters: $IC_{50}=K_i(1+S/K_m)$, with $(1+S/K_m)$ approximately 1 at low values of S/K_m.

The IC_{50} value is estimated from the data points by fitting the data to a suitable model of the enzyme inhibitor interaction. When this interaction is known to involve simple competition of the inhibitor with the substrate, a two-parameter model can be used:

$$Y=A/(1+x/B)$$

where the y is the enzyme activity measured at an inhibitor concentration of x, A is the activity in the absence of inhibitor and B is the IC_{50}. See Y.

Cheng et al., *Biochem. Pharmacol.*, *22*:3099-3108 (1973).

Effects of inhibitors of the present invention on enzymatic activity of PDE5 and PDE6 preparations as described above were assessed in either of two assays which differed from each other principally on the basis of scale and provided essentially the same results in terms of IC_{50} values. Both assays involved modification of the procedure of Wells et al., *Biochim. Biophys. Acta*, *384*:430 (1975). The first of the assays was performed in a total volume of 200 µl containing 50 mM Tris pH 7.5, 3 mM Mg acetate, 1 mM EDTA, 50 µg/mL snake venom nucleotidase and 50 nM [^{3}H]-cGMP (Amersham). Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The assays were incubated for 30 minutes at 30°C and stopped by addition of 800 µl of 10 mM Tris pH 7.5, 10 mM EDTA, 10 mM theophylline, 0.1 mM adenosine, and 0.1 mM guanosine. The mixtures were loaded on to 0.5 mL QAE Sephadex columns, and eluted with 2 mL of 0.1 M formate (pH 7.4). The eluted radioactivity was measured by scintillation counting in Optiphase Hisafe 3.

A second, microplate, PDE assay was developed using Multiscreen plates and a vacuum manifold. The assay (100 µl) contained 50 mM Tris pH 7.5, 5 mM Mg acetate, 1 mM EDTA and 250 µg/mL snake venom nucleotidase. The other components of the reaction mixture were as described above. At the end of the incubation, the total volume of the assays were loaded on a QAE Sephadex microcolumn plate by filtration. Free radioactivity was eluted

with 200 µl of water from which 50 µl aliquots were analyzed by scintillation counting as described above.

The following examples are presented to further illustrate the preparation of the claimed invention. The scope of the present invention is not to be construed as merely consisting of the following examples.

Example 1

Compound (I) was prepared as described in U.S. patent 5,859,006 and formulated in tablets using wet granulation. Povidone was dissolved in water to make a 10% solution. The active compound, microcrystalline cellulose, croscarmellose sodium, and sodium lauryl sulfate were added to a high shear mixer and mixed for 2 minutes. The powders were wet granulated with the povidone solution and extra water as required to complete the granulation. The resultant mixture was dried in a fluid bed drier with inlet air at 70°C ± 5°C until the loss on drying was below 2.5%. The granules were passed through a Comil with a suitable screen (or a sieve) and added to a suitable mixer. The extragranular croscarmellose sodium and sodium lauryl sulfate, and the colloidal anhydrous silica were passed through a suitable sieve (e.g., 500 micron) and added to the mixer and blended 5 minutes. Magnesium stearate was added and blended for 2 minutes. The blend was compressed to a target compression/weight of 250 mg using 9 mm round normal concave tooling.

The core tablets were coated with an aqueous suspension of Opadry OY-S-7322 using an Accelacota (or similar coating pan) using inlet air at 50°C to 70°C until the tablet weight was increased by approximately 8 mg. Opadry OY-S-7322 contains methylhydroxypropylcellulose Ph.Eur., titanium dioxide Ph. Eur., Triacetin USP. Opadry increases the weight of each tablet to about 258 mg. The amount of film coat applied per tablet may be less than that stated depending on the process efficiency.

The tablets are filled into blister packs and accompanied by package insert describing the safety and efficacy of the compound.

Component	Formulations (mg per tablet)	
Selective PDE5 Inhibitor[1)]	1	5
Hydroxypropyl Methylcellulose Phthalate	1	5
Microcrystalline Cellulose	221.87	213.87
Croscarmellose Sodium	5.00	5.00
Sodium Lauryl Sulfate	2.50	2.50
Povidone K30	9.38	9.38
Purified Water, USP (water for irrigation)	q.s.	q.s.
Croscarmellose Sodium	5.00	5.00
Sodium Lauryl Sulfate	2.50	2.50
Colloidal Anhydrous Silica	0.50	0.50
Magnesium Stearate	1.25	1.25
Total core subtotal	250.00	250.00
(Film coat Opadry OY-S-7322)	about 8 mg	about 8 mg

[1)] Compound (I).

Example 2

The following formula is used in preparing the finished dosage form containing 10 mg of Compound (I).

Ingredient	Quantity (mg)
Granulation	
Selective PDE5 Inhibitor[1)]	10.00
Lactose Monohydrate	153.80
Lactose Monohydrate (spray dried)	25.00
Hydroxypropylcellulose	4.00
Croscarmellose Sodium	9.00
Hydroxypropylcellulose (EF)	1.75
Sodium Lauryl Sulfate	0.70
	35.00
Outside Powders	
Microcrystalline Cellulose (granular-102)	37.50
Croscarmellose Sodium	7.00
Magnesium Stearate (vegetable)	1.25
	Total 250 mg
Film coat (approximately)	11.25

Purified Water, USP is used in the manufacture of the tablets. The water is removed during processing and minimal levels remain in the finished product.

Tablets are manufactured using a wet granulation process. A step-by-step description of the process is as follows. The drug and excipients to be granulated are security sieved. The selective

PDE5 inhibitor is dry blended with lactose monohydrate (spray dried), hydroxypropylcellulose, croscarmellulose sodium, and lactose monohydrate. The resulting powder blend is granulated with an aqueous solution of hydroxypropylcellulose and sodium lauryl sulfate using a Powrex or other suitable high shear granulator. Additional water can be added to reach the desired endpoint. A mill can be used to delump the wet granulation and facilitate drying. The wet granulation is dried using either a fluid bed dryer or a drying oven. Once the material is dried, it can be sized to eliminate any large agglomerates. Microcrystalline cellulose, croscarmellose sodium, and magnesium stearate are security sieved and added to the dry sized granules. These excipients and the dry granulation are mixed until uniform using a tumble bin, ribbon mixer, or other suitable mixing equipment. The mixing process can be separated into two phases. The microcrystalline cellulose, croscarmellose sodium, and the dried granulation are added to the mixer and blended during the first phase, followed by the addition of the magnesium stearate to this granulation and a second mixing phase.

The mixed granulation then is compressed into tablets using a rotary compression machine. The core tablets are film coated with an aqueous suspension of the appropriate color mixture in a coating pan (e.g., Accela Cota). The coated tablets can be lightly dusted with talc to improve tablet handling characteristics.

The tablets are filled into plastic containers (30 tablets/container) and accompanied by

package insert describing the safety and efficacy of the compound.

Example 3

The following formula is used in preparing a finished dosage form containing 5 mg of Compound (I).

Ingredient	Quantity (mg)
Granulation	
Selective PDE5 Inhibitor[1)]	2.50
Lactose Monohydrate	79.395
Lactose Monohydrate (spray dried)	12.50
Hydroxypropylcellulose	2.00
Croscarmellose Sodium	4.50
Hydroxypropylcellulose (EF)	0.875
Sodium Lauryl Sulfate	0.35
Outside Powders	
Microcrystalline Cellulose (granular-102)	18.75
Croscarmellose Sodium	3.50
Magnesium Stearate (vegetable)	0.63
	Total 125 mg
Film coat (approximately)	6.875

The dosage form of Example 3 was prepared in an identical manner to the dosage form of Example 2.

Example 4

Solution Capsule		
Ingredient	**mg/capsule**	**Percent (%)**
Selective PDE5 Inhibitor[1)]	10	2
PEG400 NF	490	98
Fill Weight	500	100

The gelatin capsules are precisely filled by pumping an accurate fill volume of pre-dissolved drug formulation into the partially sealed cavity of a capsule. Immediately following injection fill of the drug solution formulation, the capsule is completely heat sealed.

The capsules are filled into plastic containers and accompanied by a package insert.

Example 5

This study was a randomized, double-blind, placebo-controlled, two-way crossover design clinical pharmacology drug interaction study that evaluated the hemodynamic effects of concomitant administration of a selective PDE5 inhibitor (i.e., Compound (I)) and short-acting nitrates on healthy male volunteers. In this study, the subjects received either Compound (I) at a dose of 10 mg or a placebo, daily for seven days. On the sixth or seventh day, the subjects received sublingual nitroglycerin (0.4 mg) while supine on a tilt table. The nitroglycerin was administered 3 hours after Compound (I) dosing, and all subjects kept the nitroglycerine tablet

under their tongue until it completely dissolved. The subjects were tilted to 70° head-up every 5 minutes for a total of 30 minutes with measurement of blood pressure and heart rate. There were no discontinuations among the twenty-two healthy male subjects (ages 19 to 60 years old) that entered this study.

In a preliminary analysis of this study, Compound (I) was well tolerated and there were no serious adverse events. There were no Compound (I) changes in laboratory safety assessments or 12-lead ECGs. The most common adverse events were headache, dyspepsia, and back pain. Compound (I) demonstrated minimal, if any, effect on mean systolic blood pressure, and mean maximal nitroglycerin-induced decrease in systolic blood pressure.

Example 6

In two randomized, double-blinded placebo controlled studies, Compound (I) was administered to patients in need thereof at a range of doses, in both daily dosing and for on demand therapy, for sexual encounters and intercourse in the home setting. Doses from 5 to 20 mg of Compound (I) were efficacious and demonstrated less than 1% flushing and no reports of vision abnormalities. It was found that a 10 mg dose of Compound (I) was fully efficacious and demonstrated minimal side effects.

Enhanced erectile function was determined by the International Index of Erectile Function (IIEF) (Rosen et al., *Urology, 49*, pp. 822-830

(1997)), diaries of sexual attempts, and a global satisfaction question. Compound (I) significantly improved the percentage of successful intercourse attempts including the ability to attain and maintain an erection in both "on demand" and daily dosing regimens.

Example 7

A third clinical study was a randomized, double-blind, placebo-controlled study of Compound (I) administered "on demand" to patients with male erectile dysfunction. Compound (I) was administered over a period of eight weeks in the treatment of male erectile dysfunction (ED). Erectile dysfunction (ED) is defined as the persistent inability to attain and/or maintain an erection adequate to permit satisfactory sexual performance. "On demand" dosing is defined as intermittent administration of Compound (I) prior to expected sexual activity.

The study population consisted of 212 men, at least 18 years of age, with mild to severe erectile dysfunction. Compound (I) was orally administered as tablets of coprecipitate made in accordance with Butler U.S. Patent No. 5,985,326. Compound (I) was administered in 2 mg, 5 mg, 10 mg, and 25 mg doses, "on demand" and not more than once every 24 hours. Treatment with all nitrates, azole antifungals (e.g., ketoconazole or itraconazole), warfarin, erythromycin, or antiandrogens was not allowed at any time during the study. No other approved or experimental medications, treatments, or

devices used to treat ED were allowed. Forty-one subjects were administered a placebo.

The two primary efficacy variables were the ability of a subject to penetrate his partner and his ability to maintain an erection during intercourse, as measured by the International Index of Erectile Function (IIEF). The IIEF Questionnaire contains fifteen questions, and is a brief, reliable measure of erectile function. See R.C. Rosen et al., *Urology, 49*, pp. 822-830 (1997).

Secondary efficacy variables were IIEF domain scores for erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction; the patient's ability to achieve an erection, ability to insert his penis into his partner's vagina, completion of intercourse with ejaculation, satisfaction with the hardness of his erection, and overall satisfaction, all as measured by the Sexual Encounter Profile (SEP) diary; and a global assessment question asked at the end of the treatment period. The SEP is a patient diary instrument documenting each sexual encounter during the course of the study.

The safety aspect of the study included all enrolled subjects, and was assessed by evaluating all reported adverse events, and changes in clinical laboratory values, vital signs, physical examination results, and electrocardiogram results.

At endpoint, patients who rated their penetration ability (IIEF Question 3) as "almost always or always" were as follows: 17.5% in the placebo group, 38.1% in the 2 mg group, 48.8% in the 5 mg group, 51.2% in the 10 mg group, and 83.7% in

the 25 mg group. Comparisons revealed statistically significant differences in change in penetration ability between placebo and all dose levels of Compound (I).

At endpoint, patients who rated their ability to maintain an erection (IIEF Question 4) during intercourse as "almost always or always" are as follows: 10.0% in the placebo group, 19.5% in the 2 mg group, 32.6% in the 5 mg group, 39.0% in the 10 mg group, and 69.0% in the 25 mg group. Comparison revealed statistically significant differences in change in penetration ability between placebo and the three higher dose levels of Compound (I).

This study also included a safety evaluation. A treatment-emergent adverse event is defined as a condition not present at baseline that appeared postbaseline, or a condition present at baseline that increased in severity postbaseline. The most commonly reported treatment-emergent adverse events were headache, dyspepsia, and back pain. The incidence of treatment-emergent adverse events appeared related to dose.

Overall, this study demonstrated that all four doses of Compound (I), namely 2 mg, 5 mg, 10 mg, and 25 mg, taken "on demand" produced significant improvement, relative to placebo, in the sexual performance of men with erectile dysfunction as assessed by the IIEF, by patient diaries assessing frequency of successful intercourse and intercourse satisfaction, and by a global assessment.

The combined results from clinical studies showed that administration of Compound (I) effectively treats male erectile dysfunction, as illustrated in the following table.

IIEF ERECTILE FUNCTION DOMAIN (Change from Baseline)			
Unit Dose of Compound (I)	**n**	**Mean ± SD**	**p**
placebo	131	0.8 ± 5.3	
2 mg	75	3.9 ± 6.1	<.001
5 mg	79	6.6 ± 7.1	<.001
10 mg	135	7.9 ± 6.7	<.001
25 mg	132	9.4 ± 7.0	<.001
50 mg	52	9.8 ± 5.5	<.001
100 mg	49	8.4 ± 6.1	<.001

n is number of subjects, SD is standard deviation.

However, it also was observed from the combined clinical studies that the percent of treatment-emergent adverse events increased with an increasing unit dose of Compound (I), as illustrated in the following table:

Treatment-Emergent Adverse Events (%)							
	Unit Dose of Compound (I) (mg)						
Event	Placebo	2	5	10	25	50	100
Headache	10	12	10	23	29	34	46
Dyspepsia	6	3	14	13	19	20	25
Back Pain	5	3	3	15	18	24	22
Myalgia	3	0	3	9	16	20	29
Rhinitis	3	7	3	4	4	0	2
Conjunctivitis	1	0	1	1	0	2	5
Eyelid Edema	0	0	0	1	1	2	3
Flushing	0	0	0	<1	0	3	7
Vision Abnormalities	0	0	0	0	0	0	0

The above table shows an increase in adverse events at 25 mg through 100 mg unit doses. Accordingly, even though efficacy in the treatment of ED was observed at 25 mg to 100 mg doses, the adverse events observed from 25 mg to 100 mg doses must be considered.

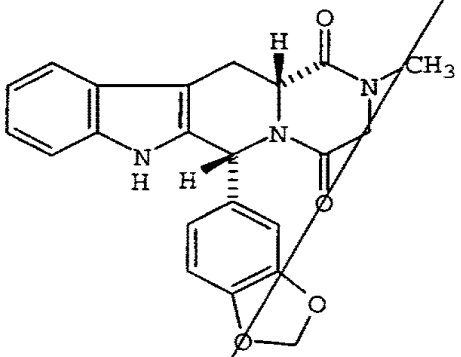
In accordance with the present invention, a unit dose of about 1 to about 20 mg, preferably about 2 to about 20 mg, more preferably about 5 to about 20 mg, and most preferably about 5 to about 15 mg, of Compound (I), administered up to a maximum of 20 mg per 24-hour period, both effectively treats ED and minimizes or eliminates the occurrence of adverse side effects. Importantly, no vision abnormalities were reported and flushing was essentially eliminated. Surprisingly, in addition to treating ED, with at about 1 to about 20 mg unit dose Compound (I), with a minimum of adverse side effects, individuals undergoing nitrate therapy also can be

treated for ED by the method and composition of the present invention.

The principles, preferred embodiments, and modes of operation of the present invention have been described in the foregoing specification. The invention intended to be protected herein, however, is not construed to be limited to the particular forms disclosed, because they are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention.

WHAT IS CLAIMED IS:

1. A pharmaceutical unit dosage composition comprising about 1 to about 20 mg of a compound having the structural formula:



said unit dosage form suitable for oral administration.

2. The dosage form of claim 1 comprising about 2 to about 20 mg of the compound in unit dosage form.

3. The dosage form of claim 1 comprising about 5 to about 20 mg of the compound in unit dosage form.

4. The dosage form of claim 2 comprising about 2.5 mg of the compound in unit dosage form.

5. The dosage form of claim 3 comprising about 5 mg of the compound in unit dosage form.

6. The dosage form of claim 3 comprising about 10 mg of the compound in unit dosage form.

7. The dosage form of claims 1 through 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

8. The dosage form of claims 1 through 6 wherein the unit dose is in the form of a tablet.

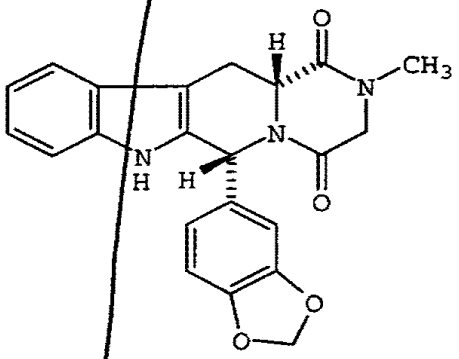
9. The dosage form of claims 1 through 6 for use in treating a condition where inhibition of PDE5 is desirable.

10. The dosage form of claim 9 wherein the condition is a sexual dysfunction.

11. The dosage form of claim 10 wherein the sexual dysfunction is male erectile dysfunction.

12. The dosage form of claim 10 wherein the sexual dysfunction is female arousal disorder.

13. A method of treating sexual dysfunction in a patient in need thereof comprising administering one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day, of a compound having the structure



14. The method of claim 13 wherein the unit dose contains about 2 to about 20 mg of the compound.

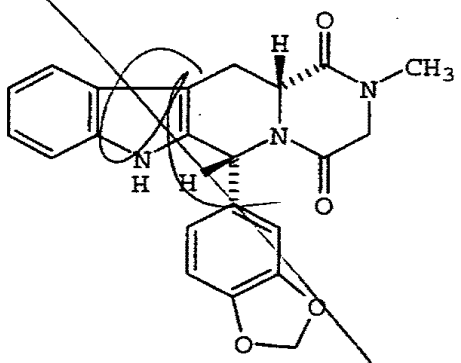
15. The method of claim 13 wherein the unit dose contains about 5 mg of the compound.

16. The method of claim 13 wherein the unit dose contains about 10 mg of the compound and is administered once per day.

17. The method of claim 13 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

18. The invention as hereinbefore described.

19. Use of a unit dose containing about 1 to about 20 mg of a compound having the structure



for the manufacture of a medicament for the treatment of sexual dysfunction in a patient in need thereof.

PCT

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(71) Applicant *(for all designated States except US)*: LILLY ICOS LLC [US/US]; 1209 Orange Street, Wilmington, DE 19801 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PULLMAN, William, Ernest [US/US]; 3004 Towne Drive, Carmel, IN 46032 (US). WHITAKER, John, Steven [US/US]; 19340 162nd Avenue, Woodinville, WA 98072 (US).

(74) Agent: NAPOLI, James, J.; Marshall, O'Toole, Gerstein, Murray & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago, IL 60606 (US).

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(54) Title: UNIT DOSAGE FORM

(57) Abstract

The present invention relates to highly selective phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manufacture. In particular, the present invention relates to potent inhibitors of cyclic guanosine 3',5'–monophosphate specific phosphodiesterase type 5 (PDE5) that when incorporated into a pharmaceutical product at about 1 to about 20 mg unit dosage are useful for the treatment of sexual dysfunction.

DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "**UNIT DOSAGE FORM**," the specification of which (check one): ☐ is attached hereto; ☐ was filed on _____ _____ as Application Serial No. _____ and was amended on _____ (if applicable); ☒ was filed as PCT International Application No. PCT/US00/11129 on April 26, 2000, and was amended under Article 19 on _____ (if applicable). I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

			Priority Claimed	
PCT/US00/11129	PCT	26/04/00	☒ Yes	☐ No
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I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

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I hereby 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 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: I hereby appoint as my attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

John B. Lungmus(18,566)	Richard H. Anderson (26,526)	Martin J. Hirsch (32,237)	James A. Flight (37,622)
Allen H. Gerstein (22,218)	Patrick D. Ertel (26,877)	James J. Napoli (32,361)	Roger A. Heppermann (37,641)
Nate F. Scarpelli (22,320)	Richard B. Hoffman(26,910)	Richard M. La Barge (32,254)	David A. Gass (38,153)
24 Michael F. Borun (25,447)	James P. Zeller (28,491)	Douglass C. Hochstetler (33,710)	Gregory C. Mayer (38,238)
Trevor B. Joike (25,542)	Kevin D. Hogg (31,839)	Robert M. Gerstein (34,824)	Michael R. Weiner (38,359)
Carl E. Moore, Jr. (26,487)	Jeffrey S. Sharp (31,879)	Anthony G. Sitko (36,278)	William K. Merkel (40,725)

Send correspondence to: James J. Napoli

FIRM NAME	PHONE NO.	STREET	CITY & STATE	ZIP CODE
Marshall, Gerstein & Borun	312-474-6300	6300 Sears Tower 233 South Wacker Drive	Chicago, Illinois	60606-6402

Full Name of First or Sole Inventor William Ernest Pullman	Citizenship ~~United States of America~~ AUSTRALIA
Residence Address - Street 42 Annin Road	Post Office Address - Street 42 Annin Road
City (Zip) Far Hills (07931) NJ	City (Zip) Far Hills (07931)
State or Country New Jersey	State or Country New Jersey
Date ☒ 11/10/01	Signature ☒

Second Joint Inventor, if any John Steven Whitaker	Citizenship United States of America
Residence Address - Street 19340 162nd Avenue	Post Office Address - Street 19342 162nd Avenue
City (Zip) Woodinville (98072)	City (Zip) Woodinville (98072)
State or Country Washington	State or Country Washington
Date ☒	Signature ☒

Third Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Fourth Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

(2) Over

37 CFR 1.56. DUTY OF DISCLOSURE - INFORMATION MATERIAL TO PATENTABILITY (Applicable Portion)

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and
(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentability defines, to make sure that any material information contained therein is disclosed to the Office.

Information relating to the following factual situations enumerated in 35 USC 102 and 103 may be considered material under 37 CFR 1.56(a).

35 U.S.C. 102. CONDITIONS FOR PATENTABILITY: NOVELTY AND LOSS OF RIGHT TO PATENT

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or

(f) he did not himself invent the subject matter sought to be patented, or

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C. 103. CONDITIONS FOR PATENTABILITY; NON-OBVIOUS SUBJECT MATTER (Applicable Portion)

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35 U.S.C. 112. SPECIFICATION (Applicable Portion)

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Atty. Docket No. 29342/36206A
184.PCT

DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "**UNIT DOSAGE FORM**," the specification of which (check one): ☐ is attached hereto; ☐ was filed on _____ _____ as Application Serial No. _____ and was amended on _____ (if applicable); ☒ was filed as PCT International Application No. PCT/US00/11129 on April 26, 2000, and was amended under Article 19 on _____ (if applicable). I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

			Priority Claimed	
PCT/US00/11129	PCT	26/04/00	☒ Yes	☐ No
(Application Serial Number)	(Country)	(Day/Month/Year Filed)		
			☐ Yes	☐ No
(Application Serial Number)	(Country)	(Day/Month/Year Filed)		

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

60/132,036	30/04/99
(Application Serial Number)	(Day/Month/Year Filed)
(Application Serial Number)	(Day/Month/Year Filed)

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or PCT international application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(Application Serial Number)	(Day/Month/Year Filed)	(Status-Patented, Pending or Abandoned)
(Application Serial Number)	(Day/Month/Year Filed)	(Status-Patented, Pending or Abandoned)

I hereby 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 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: I hereby appoint as my attorneys, with full powers of substitution and revocation, to prosecute this application and transact all busine[redacted] the Patent and Trademark Office connected th[redacted]ith:

John B. Lungmus(18,566)	Richard H. Anderson (26,526)	Martin J. Hirsch (32,237)	James A. Flight (37,622)
Allen H. Gerstein (22,218)	Patrick D. Ertel (26,877)	James J. Napoli (32,361)	Roger A. Heppermann (37,641)
Nate F. Scarpelli (22,320)	Richard B. Hoffman(26,910)	Richard M. La Barge (32,254)	David A. Gass (38,153)
Michael F. Borun (25,447)	James P. Zeller (28,491)	Douglass C. Hochstetler (33,710)	Gregory C. Mayer (38,238)
Trevor B. Joike (25,542)	Kevin D. Hogg (31,839)	Robert M. Gerstein (34,824)	Michael R. Weiner (38,359)
Carl E. Moore, Jr. (26,487)	Jeffrey S. Sharp (31,879)	Anthony G. Sitko (36,278)	William K. Merkel (40,725)

Send correspondence to: James J. Napoli

FIRM NAME	PHONE NO.	STREET	CITY & STATE	ZIP CODE
Marshall, Gerstein & Borun	312-474-6300	6300 Sears Tower 233 South Wacker Drive	Chicago, Illinois	60606-6402

Full Name of First or Sole Inventor	Citizenship
William Ernest Pullman	United States of America
Residence Address - Street	Post Office Address - Street
3004 Towne Drive	3004 Towne Drive
City (Zip)	City (Zip)
Carmel (46032)	Carmel (46032)
State or Country	State or Country
Indiana	Indiana
Date ☒	Signature ☒

Second Joint Inventor, if any	Citizenship
John Steven Whitaker	United States of America
Residence Address - Street	Post Office Address - Street
19340 162nd Avenue	19342 162nd Avenue
City (Zip)	City (Zip)
Woodinville (98072) WA	Woodinville (98072)
State or Country	State or Country
Washington	Washington
Date ☒ 11 Oct 2001	Signature ☒

2-00

Third Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

Fourth Joint Inventor, if any	Citizenship
Residence Address - Street	Post Office Address - Street
City (Zip)	City (Zip)
State or Country	State or Country
Date ☒	Signature ☒

APPLICABLE RULES AND STATUTES

37 CFR 1.56. DUTY OF DISCLOSURE - INFORMATION MATERIAL TO PATENTABILITY (Applicable Portion)

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

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(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentability defines, to make sure that any material information contained therein is disclosed to the Office.

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(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraph (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or

(f) he did not himself invent the subject matter sought to be patented, or

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C. 103. CONDITIONS FOR PATENTABILITY; NON-OBVIOUS SUBJECT MATTER (Applicable Portion)

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Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35 U.S.C. 112. SPECIFICATION (Applicable Portion)

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

PATENT APPLICATION FEE DETERMINATION RECORD

Effective O[illegible]er 1, 200[illegible]

Application or Docket Number: **10/031556**

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR 17	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	46 minus 20=	* 26
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☑

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	445	OR	BASIC FEE	890
X$ 9=		OR	X$18=	468
X42=		OR	X84=	
+140=		OR	+280=	280
TOTAL		OR	TOTAL	1638

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 15	Minus	** 46	=
Independent	* 2	Minus	*** 3	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 11	Minus	** 46	= —
Independent	* 1	Minus	*** 3	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	—
X40=		OR	X80=	—
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	—

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X40=		OR	X80=	
+135=		OR	+270=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

PATENT APPLICATION SERIAL NO. 10/031556

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

01/28/2002 SNAJARRO 00000102 10031556

01 FC:970 890.00 OP

03/25/2002 IEVANS 00000001 132855 10031556

01 FC:968 280.00 CH
02 FC:966 468.00 CH

PTO-1556
(5/87)

*U.S. GPO: 2000-468-987/39595

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO. 10/031556

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2		1				
3		1				
4		1				
5		1				
6		1				
7		6				
8		6				
9		6				
10		6				
11		6				
12		6				
13	1					
14		1				
15		1				
16		1				
17		1				
18	X	X				
19	X	X				
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48						
49						
50						
TOTAL IND.	1					
TOTAL DEP.	45					
TOTAL CLAIMS	46					

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
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94						
95						
96						
97						
98						
99						
100						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

PT. (7-78)

*MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

U.S. DEPARTMENT of COMMERCE
Patent and Trademark Office

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants:

WILLIAM E. PULLMAN ET AL.

U.S. National Phase of PCT/US00/11129 filed April 26, 2000

Filed: Herewith

For: **UNIT DOSAGE FORM**

Group Art Unit: Unassigned

Examiner: Unassigned

Attorney Docket No. 29342/36206A

"EXPRESS MAIL" mailing label No. **EK657817671US**

Date of Deposit: **October 19, 2001**

I hereby certify that this paper (or fee) is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 CFR §1.10 on the date indicated above and is addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Richard Zimmermann

PRELIMINARY AMENDMENT
ACCOMPANYING APPLICATION TRANSMITTAL

Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend the above-identified application as follows:

IN THE SPECIFICATION:

Page 1, after the title, please delete the CROSS-REFERENCE TO RELATED APPLICATION in its entirety and insert therefor:

--CROSS-REFERENCE TO RELATED APPLICATIONS

A1

This is the U.S. national phase application of International Application No. PCT/US00/11129, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/132,036, filed April 30, 1999.--

IN THE CLAIMS:

Cancel claims 18 and 19 without prejudice.

Amend claims 7-9 as follows:

A2

7. (Amended) The dosage form of claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

8. (Amended) The dosage form of claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in the form of a tablet.

9. (Amended) (Amended) The dosage form of claim 1, 2, 3, 4, 5, or 6 for use in treating a condition wherein inhibition of PDE5 is desirable.

REMARKS

Claims 1-19 are pending in the application. Claims 18 and 19 have been cancelled. Therefore, claims 1-17 are at issue in this application.

The amendments are described in more detail below. Pursuant to 37 C.F.R. §1.121, a marked-up version of the changes made to the claims by the present amendment is attached hereto following the signature page of this amendment. The first page of the marked-up version of the changes is captioned "Version With Markings to Show Changes Made."

This preliminary amendment adds no new matter. The specification has been amended to insert a cross-reference to a related application. Claims 7-9 have been amended to improve the form of the claims.

It is submitted that the amendment should be entered, and that the claims are of a proper form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

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
October 19, 2001

Version With Markings to Show Changes Made
(U.S. National Stage of PCT/US00/11129
filed October 19, 2001)

IN THE SPECIFICATION:

The following cross-reference to related application has been inserted into the specification:

CROSS-REFERENCE TO RELATED APPLICATIONS

This is the U.S. national phase application of International Application No. PCT/US00/11129, filed on April 26, 2000, which claims the benefit of provisional patent application Serial No. 60/132,036, filed April 30, 1999.

IN THE CLAIMS:

Claims 18 and 19 have been cancelled without prejudice.

Claims 7-9 have been amended as follows:

7. (Amended) The dosage form of [claims 1 through 6] claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

8. (Amended) The dosage form of [claims 1 through 6] claim 1, 2, 3, 4, 5, or 6 wherein the unit dose is in the form of a tablet.

9. (Amended) The dosage form of [claims 1 through 6] claim 1, 2, 3, 4, 5, or 6 for use in treating a condition wherein inhibition of PDE5 is desirable.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 27 November 2000 (27.11.00)	
International application No. PCT/US00/11129	**Applicant's or agent's file reference** 29342/36206
International filing date (day/month/year) 26 April 2000 (26.04.00)	**Priority date** (day/month/year) 30 April 1999 (30.04.99)
Applicant PULLMAN, William, Ernest et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 November 2000 (02.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
29342/36206		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/11129	26/04/2000	30/04/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant LILLY ICOS LLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/11/2000	25.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Veronese, A Telephone No. +49 89 2399 7824

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/11129

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-32 as originally filed

Claims, No.:

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 13-17 (IA).

because:

   ☒ the said international application, or the said claims Nos. 13-17 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-12,18,19

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability.

Claims 13-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). However, although not required under the provisions of the PCT, an opinion will be given with respect to novelty and inventive step.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INVENTIVE STEP

Reference is made to the following documents:

D1: WO 97 03675 A (GLAXO WELLCOME LAB SA ;DAUGAN ALAIN CLAUDE MARIE (FR)) 6 February 1997 (1997-02-06)

D2: ISRAEL M: 'VIAGRA: THE FIRST ORAL TREATMENT FOR IMPOTENCE' PHARMACEUTICAL JOURNAL,PHARMACEUTICAL SOCIETY, LONDON,GB, vol. 261, 1 August 1998 (1998-08-01), pages 164-165, XP000919343 ISSN: 0031-6873

D1, see page 5 lines 4-14, example 1 (compound A) at page 10, the pharmaceutical formulations at pages 12-16 and claim 2 disclose the use of pharmaceutical unit dosages comprising the PDE5 inhibitor (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 (Compound I) for the treatment of erectile dysfunctions. Compositions comprising 50 mg of compound I are shown and concentration ranges from 0.2 to 400 mg are indicated as suitable for oral administration. Compositions in the claimed range of 1 to 20 mg are therefore also considered to be implicitly disclosed.

If a novelty objection could be overcome, the selection of pharmaceutical unit dosages comprising 1 to 20 mg of Compound I as in the present invention can not however considered to involve an inventive step.
The routine experimentation to optimise the required amounts of ingredients of known compositions for a known use falls within the normal capacity of the average skilled person. Even if the claimed compositions provide some benefits when compared to the compositions of the prior art, the experimental data reported in the present application are not characterized by any new or surprising effect.
Furthermore, for the patient treatment it is not the "unit dose" which is important to provide a certain medical effect, but the dose which is practically administered. For example two tablets or half tablet could be administered to the patient to adjust the dosage and obtain a certain effect.
The IPEA is therefore of the opinion that the subject-matter underlying claims 1-11, 13- 19 does not involve an inventive step in the sense of Art. 33(3) PCT.

Also claim 12 , claiming the use of the PDE5 diesterase inhibitor I, for the treatment of sexual disfunctions in woman is not considered to involve an inventive step in view of document D2, which disclose the use of PDE5 inhibitor VIAGRA for the treatment of sexual disfunctions in females, see page 165, column 2.

INDUSTRIAL APPLICATION

For the assessment of the present claims 13-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited (Rule 70.10)
WO9959584, which has been disregarded in writing the present Report, could become relevant for the assessment of novelty under some patent law systems. Priorities have not been checked.

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO9959584	25 November 1999	17 May 1999	20 May 1998

Re Item VIII

Certain observations on the international application

Claim 9 defines the subject-matter to be protected by way of the biological mechanism underlying the action of the disclosed compounds. This expression does not specify specific diseases recognized in the art to which the invention pertains and is not considered to fulfill the requirements of Art 6 PCT. The claim has been therefore examined under the assumption that the conditions indicated in claims 10-12 are intended.

The relative term "about" used in claims 1-6, 13-19 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

Claim 18 does not seem to define any additional subject matter and therefore does not comply with the requirements of conciseness of Art. 6 PCT.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
29342/36206		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 11129	26/04/2000	30/04/1999
Applicant		
LILLY ICOS LLC et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   COMPOSITIONS COMPRISING PHOSPHODIESTERASE INHABITORS FOR THE TREATMENT OF SEXUAL DISFUNCTION

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/11129

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4985 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 03675 A (GLAXO WELLCOME LAB SA ;DAUGAN ALAIN CLAUDE MARIE (FR)) 6 February 1997 (1997-02-06) page 3, line 11,12 page 3, line 24,25 page 5, line 4-11 claims; examples 1,3 ---	1-19
P,X	WO 99 59584 A (ESTOK THOMAS MARK ;SCHERING CORP (US)) 25 November 1999 (1999-11-25) page 4, last paragraph page 42, line 11,12 page 61, line 20,21 claim 20 --- -/--	1-19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2000	28/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/11129

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 19978 A (GLAXO LAB SA ;DAUGAN ALAIN CLAUDE MARIE (FR)) 27 July 1995 (1995-07-27) cited in the application page 8, line 5-15; example 78 page 80, line 21,22 page 80, last paragraph claims 10,12,14	1-12
P,X	DATABASE WPI Section Ch, Week 200029 Derwent Publications Ltd., London, GB; Class B02, AN 2000-339026 XP002152606 & WO 00 20033 A (EISAI CO LTD), 13 April 2000 (2000-04-13) abstract	1-12
A	ISRAEL M: "VIAGRA: THE FIRST ORAL TREATMENT FOR IMPOTENCE" PHARMACEUTICAL JOURNAL,PHARMACEUTICAL SOCIETY, LONDON,GB, vol. 261, 1 August 1998 (1998-08-01), pages 164-165, XP000919343 ISSN: 0031-6873 page 164, column 1-2	1-19
A	GOLDENBERG M M: "SAFETY AND EFFICACY OF SILDENAFIL CITRATE IN THE TREATMENT OF MALE ERECTILE DYSFUNCTION" CLINICAL THERAPEUTICS,US,EXCERPTA MEDICA, PRINCETON, NJ, vol. 20, no. 6, 1998, pages 1033-1048, XP000853855 ISSN: 0149-2918 page 1041, column 1 -page 1042, column 1	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/11129

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/11129

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703675 A	06-02-1997	AU 704955 B	13-05-1999
		AU 6419196 A	18-02-1997
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		DE 69503753 T	21-01-1999
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		US 6127542 A	03-10-2000
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		ZA 9500424 A	27-09-1995
WO 0020033 A	13-04-2000	JP 2000178204 A	27-06-2000
		JP 2000191518 A	11-07-2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 November 2000 (09.11.2000)

PCT

(10) International Publication Number
WO 00/66099 A3

(51) International Patent Classification[7]: A61K 31/4985, A61P 15/10

(21) International Application Number: PCT/US00/11129

(22) International Filing Date: 26 April 2000 (26.04.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/132,036 30 April 1999 (30.04.1999) US

(71) Applicant *(for all designated States except US)*: **LILLY ICOS LLC** [US/US]; 1209 Orange Street, Wilmington, DE 19801 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **PULLMAN, William, Ernest** [US/US]; 3004 Towne Drive, Carmel, IN 46032 (US). **WHITAKER, John, Steven** [US/US]; 19340 162nd Avenue, Woodinville, WA 98072 (US).

(74) Agent: **NAPOLI, James, J.**; Marshall, O'Toole, Gerstein, Murray & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago, IL 60606 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

(88) Date of publication of the international search report:
18 January 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS COMPRISING PHOSPHODIESTERASE INHABITORS FOR THE TREATMENT OF SEXUAL DISFUNCTION

(57) Abstract: The present invention relates to highly selective phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manufacture. In particular, the present invention relates to potent inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase type 5 (PDE5) that when incorporated into a pharmaceutical product at about 1 to about 20 mg unit dosage are useful for the treatment of sexual dysfunction.

WO 00/66099 A3

INTERNATIONAL SEARCH REPORT

[redacted] nal Application No
PCT/US 00/11129

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4985 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 03675 A (GLAXO WELLCOME LAB SA ;DAUGAN ALAIN CLAUDE MARIE (FR)) 6 February 1997 (1997-02-06) page 3, line 11,12 page 3, line 24,25 page 5, line 4-11 claims; examples 1,3 ---	1-19
P,X	WO 99 59584 A (ESTOK THOMAS MARK ;SCHERING CORP (US)) 25 November 1999 (1999-11-25) page 4, last paragraph page 42, line 11,12 page 61, line 20,21 claim 20 --- -/--	1-19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2000	28/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted]inal Application No
[redacted]CT/US 00/11129

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 19978 A (GLAXO LAB SA ;DAUGAN ALAIN CLAUDE MARIE (FR)) 27 July 1995 (1995-07-27) cited in the application page 8, line 5-15; example 78 page 80, line 21,22 page 80, last paragraph claims 10,12,14	1-12
P,X	DATABASE WPI Section Ch, Week 200029 Derwent Publications Ltd., London, GB; Class B02, AN 2000-339026 XP002152606 & WO 00 20033 A (EISAI CO LTD), 13 April 2000 (2000-04-13) abstract	1-12
A	ISRAEL M: "VIAGRA: THE FIRST ORAL TREATMENT FOR IMPOTENCE" PHARMACEUTICAL JOURNAL,PHARMACEUTICAL SOCIETY, LONDON,GB, vol. 261, 1 August 1998 (1998-08-01), pages 164-165, XP000919343 ISSN: 0031-6873 page 164, column 1-2	1-19
A	GOLDENBERG M M: "SAFETY AND EFFICACY OF SILDENAFIL CITRATE IN THE TREATMENT OF MALE ERECTILE DYSFUNCTION" CLINICAL THERAPEUTICS,US,EXCERPTA MEDICA, PRINCETON, NJ, vol. 20, no. 6, 1998, pages 1033-1048, XP000853855 ISSN: 0149-2918 page 1041, column 1 -page 1042, column 1	1-19

INTERNATIONAL SEARCH REPORT

[redacted]tion on patent family members

[redacted]nal Application No
PCT/US 00/11129

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703675 A	06-02-1997	AU 704955 B	13-05-1999
		AU 6419196 A	18-02-1997
		BR 9609758 A	26-01-1999
		CA 2226784 A	06-02-1997
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		CZ 9800033 A	13-05-1998
		EP 0839040 A	06-05-1998
		HU 9900065 A	28-05-1999
		JP 11509221 T	17-08-1999
		NO 980153 A	10-03-1998
		PL 324495 A	25-05-1998
		SK 3998 A	08-07-1998
		US 6140329 A	31-10-2000
WO 9959584 A	25-11-1999	AU 4068599 A	06-12-1999
WO 9519978 A	27-07-1995	AP 556 A	07-11-1996
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		AU 1574895 A	08-08-1995
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		FI 962927 A	19-07-1996
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		IL 112384 A	16-08-1998
		JP 9508113 T	19-08-1997
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		NZ 279199 A	26-01-1998
		PL 315559 A	12-11-1996
		RU 2142463 C	10-12-1999
		SG 49184 A	18-05-1998
		SI 740668 T	28-02-1999
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WILLIAM ERNEST PULLMAN ET AL.

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James J. Napoli
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Attorney for Applicants

INFORMATION DISCLOSURE STATEMENT

Commissioner of Patents
Washington, D.C. 20231

Sir:

Pursuant to his duty of disclosure under 37 C.F.R. §1.56, applicants hereby bring to the examiner's attention patents and publications that may be material to the examination of the above-identified application. Therefore, in compliance with 37 C.F.R. §1.97 and §1.98, applicant has enclosed a completed Form PTO-1449 listing the possibly pertinent patents and publications, and a copy of each patent and publication.

Another application related to the above-identified application is:

Applicants: Jeffrey T. Emmick et al.
Serial No. 09/558,911
Filing Date: April 26, 2000
Title: Articles of Manufacture
Status: Pending.

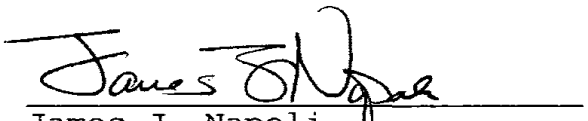
This Information Disclosure Statement is submitted more than three months after the filing date of the above-identified application, and to applicants' knowledge, before the mailing date of a first Office Action on the merits. Therefore, under 37 C.F.R. §1.97(b), this Information Disclosure Statement shall be considered by the Patent Office.

The Commissioner, however, is hereby authorized to charge any fee which may be required during the pendency of this application under 37 C.F.R. 1.16 or 37 C.F.R. 1.17 to Deposit Account No. 13-2855. A duplicate copy of this Transmittal is enclosed herewith.

A copy of the International Search Report is enclosed for the convenience of the examiner.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

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
March 14, 2002

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(71) Applicant *(for all designated States except US)*: LABORATOIRES GLAXO S.A. [FR/FR]; 42, rue Vineuse, F-75016 Paris (FR).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DAUGAN, Alain, Claude-Marie [FR/FR]; Laboratoires Glaxo S.A., Centre de Recherches, Z.A. de Courtabœuf, 25, avenue de Québec, F-91940 Les Ulis (FR).

(74) Agents: GALLAFENT, Alison et al.; Glaxo plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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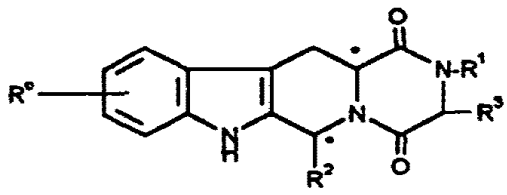

(I)

(a)

(57) Abstract

A compound of formula (I) and salts and solvates thereof, in which: R^0 represents hydrogen, halogen or C_{1-6} alkyl; R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl; R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring (a) 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 R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 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.

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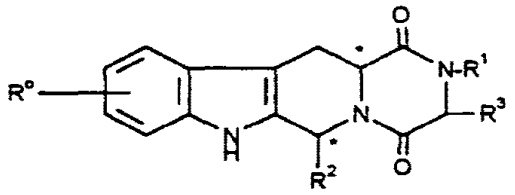
TETRACYCLIC DERIVATIVES, PROCESS OF PREPARATION AND USE

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)

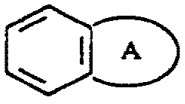


(I)

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

R^0 represents hydrogen, halogen or C_{1-6} alkyl;

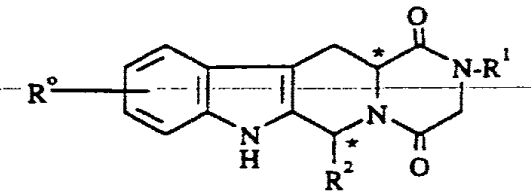
R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 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

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 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)

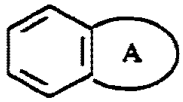


(Ia)

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

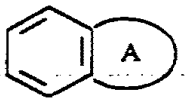
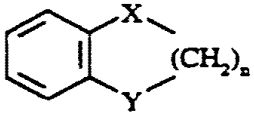
R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl; and

R^2 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 R^1 above, the term "aryl" as part of an arylC_{1-3}alkyl group means phenyl or phenyl substituted by one or more (e.g. 1, 2 or 3) substituents selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy and methylenedioxy. The term "heteroaryl" as part of a heteroarylC_{1-3}alkyl group means thienyl, furyl or pyridyl each optionally substituted by one or more (e.g. 1, 2 or 3) substituents selected from halogen, C_{1-6} alkyl and C_{1-6}alkoxy. The term "C_{3-8}cycloalkyl" as a group or part of a C_{3-8}cycloalkylC_{1-3}alkyl group means a monocyclic ring comprising three to eight carbon atoms. Examples of suitable cycloalkyl rings include the C_{3-6}cycloalkyl rings cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Within R^2 above, optional benzene ring substituents are selected from one or more (e.g. 1, 2 or 3) atoms or groups comprising halogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-CO_2R^b$, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, cyano, nitro and NR^aR^b, where R^a and R^b are each hydrogen or C_{1-6}alkyl, or R^a may also represent C_{2-7}alkanoyl or C_{1-6}alkylsulphonyl. Optional substituents for the remaining ring systems are selected from one or more (e.g. 1, 2 or 3) atoms or groups comprising halogen, C_{1-6}alkyl, C_{1-6}alkoxy and arylC_{1-3}alkyl as defined above.

The bicyclic ring  may, for example, represent naphthalen , a heterocycle such as benzoxazole, benzothiazole, benzisoxazole, benzimidazole, quinoline, indole, benzothiophene or benzofuran or  (where n is an integer 1 or 2 and X and Y may each represent CH_2, 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 C_{1-4}alkyl 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 "haloC_{1-6}alkyl" means an alkyl group 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 haloC_{1-6}alkoxy group is a haloC_{1-6}alkyl group as defined abov linked to the R^2 benzene ring via an oxygen atom. Examples of haloC_{1-6}alkyl groups include trifluoromethyl and 2,2,2-trifluoroethyl. An example of a haloC_{1-6}alkoxy group is trifluoromethoxy. The term "C_{2-7}alkanoyl" means a C_{1-6}alkylcarbonyl group where the C_{1-6}alkyl portion is as defined above. An example of a suitable C_{2-7}alkanoyl group is the C_2alkanoyl group acetyl.

It will be appreciated that when R^o is a halogen atom or a C_{1-6}alkyl 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.

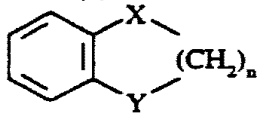
The compounds of formula (I) may contain two or more asymmetric centres and thus can exist as enantiomers or diastereoisomers. In particular, in formula (I) above two ring chiral centres are denoted with asterisks. It is to be understood that the invention includes both mixtures and separate individual 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, benzenesulphonate 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 R^0 is hydrogen or halogen (e.g. fluorine), especially hydrogen.

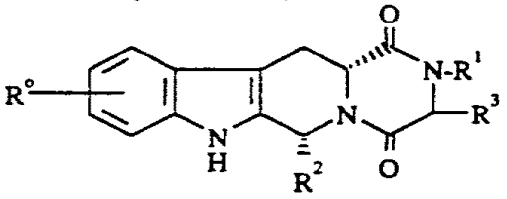
Another particular group of compounds of the invention are those compounds of formula (I) in which R^1 represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl,, C_{3-6}cycloalkyl, C_{3-6}cycloalkylmethyl, pyridylC_{1-3}alkyl, furylC_{1-3}alkyl or optionally substituted benzyl. Within this particular group of compounds, examples of C_{1-4}alkyl groups are methyl, ethyl, n-propyl, i-propyl and n-butyl. Examples of C_{3-6}cycloalkylmethyl 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 thos compounds of formula (I) in which R^2 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 ar each CH_2 or O). Within this particular group of compounds, examples of substituted benzene groups are benzene substituted by one of halogen (e.g. chlorine), hydroxy, C_{1-3}alkyl (e.g. methyl, ethyl or i-propyl), C_{1-3}alkoxy (e.g. methoxy or ethoxy), $-CO_2R^b$, halomethyl (e.g. trifluoromethyl), halomethoxy (e.g. trifluoromethoxy), cyano, nitro or NR^aR^b where R^a and R^b are each hydrogen or methyl or R^a is acetyl; or benzene substituted by dihalo (e.g. dichloro) or by C_{1-3}alkoxy (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) substituent thiophene ring.

A still further particular group of compounds of formula I are those wherein R^3 represents hydrogen or R^1 and R^3 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)



(Ib)

and mixtures thereof with their cis optical enantiomers, including racemic mixtures, and salts and solvates (e.g. hydrates) of these compounds in which R^o is hydrogen or halogen (e.g. fluorine), especially hydrogen and R^1, R^2 and R^3 are as defined previously.

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

Within the above definitions R^1 may preferably represent C_{1-4}alkyl (e.g. methyl, ethyl, i-propyl and n-butyl), C_{3-6}cycloalkyl (e.g. cyclopentyl) or C_{3-6}cycloalkylmethyl (e.g. cyclopropylmethyl).

R^2 may preferably represent a substituted benzene ring such as benzene substituted by C_{1-3}alkoxy (e.g. methoxy) or by C_{1-3}alkoxy (e.g. methoxy) and halogen (e.g. chlorine), particularly 4-methoxyphenyl or 3-chloro-4-methoxyphenyl, or R^2 may preferably represent 3,4-methylenedioxyphenyl.

It is to be understood that the present invention covers all appropriat 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[3,4-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;
(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)-pyrrolo[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-HT_1. 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 diseas , 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 0.5-800mg daily for an average adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400mg 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 carri r 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 caprylic/capric 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 invention thus provides, in another aspect, a combination of a compound of formula (I) together with another therapeutically active agent.

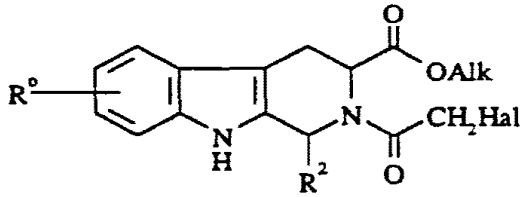
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination may also be administer d 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^o, R^1 and R^2 are as defined in formula (I) above unless otherwise indicated.

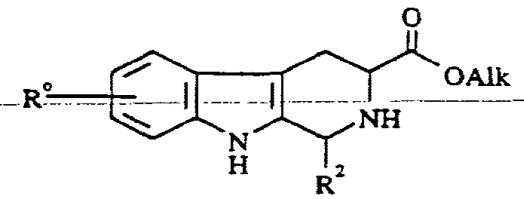
Thus, a process (A) for preparing a compound of formula (I) wherein R^3 represents hydrogen comprises treating a compound of formula (II)



(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°C to reflux (e.g. at about 50°C).

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



(III)

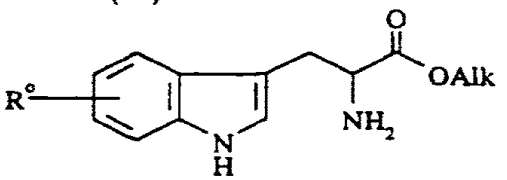
with a haloacetyl halide (e.g. chloroacetyl chloride) in a suitable solvent such as a halogenated hydrocarbon (e.g. trichloromethane or dichloromethane), or an ether (e.g. tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g. a trialkylamine such as triethylamine) or an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

Individual enantiomers of the compounds of the invention may be prepar d 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.

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



(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 est rs as appropriate.

Procedure (a)

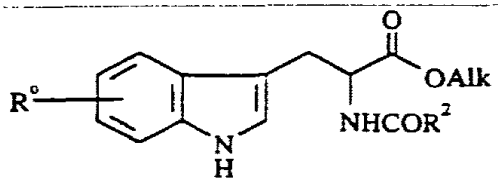
This comprises a Pictet-Spengler cyclisation between a compound of formula (IV) and an aldehyde R^2CHO. The reaction may conveniently be effected in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an aromatic hydrocarbon (e.g. toluene) in the presence of an acid such as trifluoroacetic acid. The reaction may conveniently be carried out at a temperature of from -20°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°C to the refluxing temperature of the solution. The mixture may then be subjected to chromatography (e.g. flash column chromatography) to separat 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) compris s 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

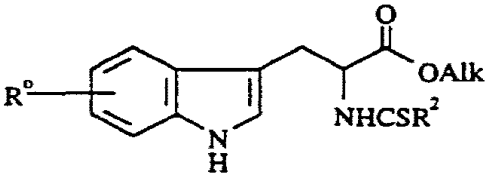
base such as a trialkylamine (for example triethylamine), to provide a compound of formula (V)



(V)

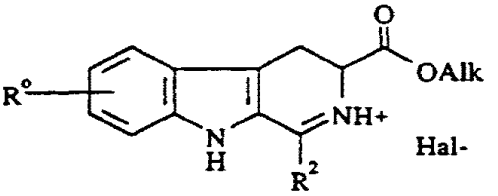
The reaction may be conveniently carried out in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an ether (e.g. tetrahydrofuran) and at a temperature of from -20°C to +40°C.

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)



(VI)

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



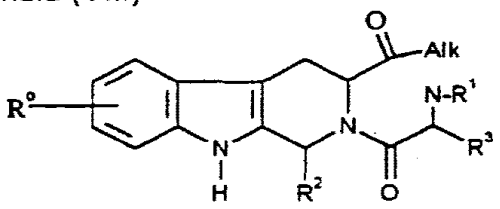
(VII)

(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 b 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).

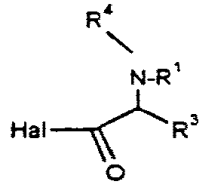
There is further provided by the present invention a process (B) for preparing a compound of formula (I), wherein R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain, which process (B) comprises cyclisation of a compound of formula (VIII)



(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 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.

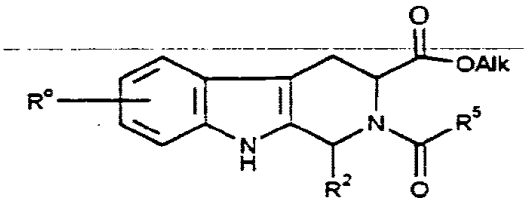
Conveniently a compound of formula (VIII) is prepared by reaction of a compound of formula (III) as hereinbefore described with a compound of formula (IX)



(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)



(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 th 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_{3-6}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 sulphonylating 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 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, R^2 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 CH_2Cl_2 (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 CH_2Cl_2 (100 mL), washed with a saturated aqueous solution of $NaHCO_3$, then with water and dried over Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography eluting with CH_2Cl_2/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.

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 ($CDCl_3$) 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, CO_2CH_3) ; 3.2 - 3.1 (ddd, 1H, H-4) 2.9 (m, 1H, H-4) ; 2.4 (brs, 1H, NH) and Intermediate 16, the trans isomer as a white solid m.p. : 204°C.

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 ^1H 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, CH_2CH_2Ar).

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 ^1H 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. : 119°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 isomers

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. : 134-137°C and Intermediate 21, the trans isomer as white crystals m.p. :169°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 isomers

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°C and Intermediate 23, the trans isomer as white crystals m.p. :182-184°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°C and Intermediate 25, the trans isomer as a cream solid m.p. : 205°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°C and Intermediate 27, the trans isomer as a cream solid m.p. : 120°C.

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°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}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, $CO_2CH_2CH_3$); 3.8 (dd, 1H, H-3); 3.2 - 2.8 (m, 2H, H-4); 2.2 (s, 3H, CH_3); 1.25 (t, 3H, $CO_2CH_2CH_3$) and Intermediate 30, the trans isomer as a cream solid m.p. : 152°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°C and Intermediate 32, the trans isomer as white crystals m.p. : 180°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 ^1H 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°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°C and Intermediate 36, the trans isomer as pale yellow crystals m.p. : 203°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, 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[3,4-b]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, CO_2CH_3) 3.1 (m, 1H, H-4) ; 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 ($CDCl_3$) 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, CO_2CH_3) ; 3.4 (ddd, 1H, H-4) ; 3.1 (m, 1H, H-4) ; 2.7 (q, 2H, $C\underline{H}_2CH_3$) 1.4 (t, 3H, $CH_2C\underline{H}_3$).

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, CO_2CH_3) ; 2.95-2.5 (m, 3H, H-4 + $C\underline{H}$-$(Me)_2$) 2.4 (brs, 1H, NH) ; 1(d, 6H, 2xCH_3) and Intermediate 44, the trans 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, 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 isomers

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 whit 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-fluoro-tryptophan 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[3,4-b]indole-3-carboxylate, cis and trans isomers

The same method but starting from racemic 5-fluoro-tryptophan methyl ester and 4-methoxybenzaldehyde gave Intermediate 52, the cis isomer as a solid 1H NMR ($CDCl_3$) 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, CO_2CH_3) ; 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 CH_2Cl_2 (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 CH_2Cl_2 (200 mL) and washed with a saturated aqueous solution of $NaHCO_3$, then with water (3x200 mL) and dried over Na_2SO_4. 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 :

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 isom r 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.
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 ($CDCl_3$) 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, CO_2CH_3); 3.3 - 2.9 (m, 2H, H-4); 2.5 (s, 3H, CH_3).
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 th corresponding hydrochloride salt in water with saturated aqueous $NaHCO_3$ solution and extraction with CH_2Cl_2) (25.7g) and piperonal (19.4g) in anhydrous dichloromethane (700ml) cooled to 0°C was added dropwise trifluoroacetic acid (18.1ml) and the solution was allowed to react at 4°C. After 5 days, the yellow solution was diluted with dichloromethane (500ml). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$, then with water (3 x 500ml) until the pH was neutral and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to a volume of about 500ml. The trans-isomer, which crystallised, was filtered and the filtrate was reduced to 200ml.

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 (11.4g).
mp : 188°C
$[\alpha]_D^{20°}$ = +32.4° (c = 1.03, $CHCl_3$).
The filtrate containing mainly the cis-isomer was reduced to 100ml and isopropyl ether (200ml) was added. Upon cooling, the (1R,3R) isomer, Intermediate 68, crystallised as a white solid (17.4g).
mp : 154-155°C
$[\alpha]_D^{20°}$ = + 24.4° (c = 1.03, $CHCl_3$).

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 (5.0g) was dissolved in methanol (150ml). 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 $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water, dried over Na_2SO_4 and purified by flash chromatography eluting with dichloromethane/methanol (99/1) to give the title compound (2.3g) corresponding to an authentic sample of Intermediate 68.

Method B
Intermediate 67 (25g) was heated in 1N hydrochloric acid (78.5ml) and water (400ml) 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 (3 x 200ml) and dried to give the hydrochloride salt of the title compound (20g) 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 (2g) was heated in 1N hydrochloric acid (6.8ml) and water (15ml) at 50°C for 72 hours. A similar work-up as described in Method B above gave the hydrochloride salt of the title compound (1.7g) as a white solid.

Intermediate 70

(R)-N$^{\alpha}$-(3,4-Methylenedioxyphenylcarbonyl)-tryptophan methyl ester

To a suspension of D-tryptophan methyl ester hydrochloride (10.2g) in anhydrous CH_2Cl_2 (150ml) cooled at 0°C was added dropwise triethylamin (12.3ml). To the resulting solution solid piperonyloyl chloride (8.16g) 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 $NaHCO_3$ and again with water. After drying over Na_2SO_4 and evaporation of the solvent under reduced presure, the resulting oil on trituration from hot cyclohexane afford d the title compound as a white solid (14.7g).

mp : 123-124°C

$[\alpha]_D^{20°}$ = - 84.4° (c = 1.04, $CHCl_3$).

Intermediate 71

(R)-N$^{\alpha}$-(3,4-Methylenedioxyphenylthiocarbonyl)-tryptophan methyl ester

A mixture of Intermediate 70 (14g) and Lawesson's reagent (9.28g) in dimethoxyethane (280ml) was heated at 60°C under N_2 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 $NaHCO_3$ and water and dried over Na_2SO_4. 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 (9.74g).

mp : 129-130°C

$[\alpha]_D^{20°}$ = - 186.8° (c = 1.14, $CHCl_3$).

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 (9g) and methyl iodide (10ml) in anhydrous dichloromethane (200ml) 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 (13.11g) was dissolved in methanol (250ml) and the solution was cooled to -78°C. $NaBH_4$ (0.99g) 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 (10ml) and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water and then with brine and dried over Na_2SO_4. 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 (5.15g) 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 (9.7g) and $NaHCO_3$ (2.79g) in anhydrous $CHCl_3$ (200ml) was added dropwise chloroacetyl chloride (5.3ml) at 0°C under N_2. The resulting mixture was stirred for 1 hour at the same temperature and diluted with $CHCl_3$ (100ml). Water (100ml) was then add d dropwise with stirring to the mixture, followed by a saturated aqueous 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, the oily compound obtained was crystallised from ether to give the title compound as a pale yellow solid (9.95g).

mp : 233°C

$[\alpha]_D^{20°} = -125.4°$ (c = 1.17, $CHCl_3$).

Method B

Chloroacetyl chloride (4ml) was added dropwide to a solution of Intermediate 72 (16.1g) and triethylamine (7ml) in anhydrous CH_2Cl_2 (200ml) at 0°C under N_2. The solution was stirred at 0°C for 30 minutes, then diluted with CH_2Cl_2 (300ml). The solution was washed with water (200ml), a saturated aqueous solution of $NaHCO_3$ (300ml) and brine (400ml). After drying over Na_2SO_4 and evaporation under reduced pressure, the resulting solid was washed with ether (300ml) to give the title compound as a pale yellow solid (18.3g).

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]oxazinyl))-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]oxazinyl))-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 4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carboxaldehyde gave Intermediate 75 the cis isomer as an oily compound ^1H 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-benzylindolinyl))-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)-R-prolyl]-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-prolyl]-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 saturat d NaCl solution and dried over Na_2SO_4. Evaporation of the solvent and

recrystallisation of the crude product from 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 crystallis d 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. mol). 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-dibenzyloxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-dibenzyloxyphenyl)-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-dibenzyloxybenzaldehyde gave intermediate 84, the cis isomer as an oily compound 1H 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}HNMR ($CDCl_3$) 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-dibenzyloxyphenyl)-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, $[\alpha]^{20°}_D$ = + 11.7° (c = 1.23 ; $CHCl_3$).

Intermediate 87

Methyl 1,2,3,4-tetrahydro-1-(5-(2-methylisoindolinyl))-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-methylisoindoline-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 $NaHCO_3$ (0.6 g) in anhydrous $CHCl_3$ (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 $CHCl_3$. Water (20 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 dri d over Na_2SO_4. After evaporation of th solvent under reduced pressur , 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 N_2 for 14 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). After washing with water (3x30 mL), drying over Na_2SO_4 and evaporating to dryness, the residue was purified by flash chromatography eluting with CH_2Cl_2/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 $C_{22}H_{19}N_3O_4$:
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 $C_{25}H_{26}FN_3O_3$ (0.1 H_2O):
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 $C_{22}H_{19}N_3O_4$:
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 $C_{21}H_{17}N_3O_4$:
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 $C_{23}H_{19}F_4N_3O_3$:
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 $C_{22}H_{18}FN_3O_4$:
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 $C_{22}H_{19}N_3O_4$ (0.25 toluene):
Calculated : C, 69.16 ; H, 5.13 ; N, 10.19;
Found : C,69.09 ; H, 5.14 ; N, 10.19%.
$[\alpha]_D^{20°}$ = -293.4° (C=1.28; $CHCl_3$).

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 $C_{22}H_{19}N_3O_4$ (0.3 toluene):
Calculated : C, 69.41 ; H, 5.17 ; N, 10.08;
Found : C, 69.56 ; H,5.24 ; N, 10.08%.
$[\alpha]_D^{20°}$ = + 297.9° (C=1.21;.$CHCl_3$).

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-(2-pyridyl)ethylamine and intermediate 1 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p. : 218-222°C.
Analysis for $C_{28}H_{24}N_4O_4$:
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 H_2O):

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 CH_2Cl_2/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 H_2O):

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 $C_{23}H_{21}N_3O_4$:
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.
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 $C_{28}H_{23}N_3O_4(1\ H_2O)$:
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 $C_{28}H_{22}FN_3O_4$:

Calculated: C,69.56;H,4.59;F,3.93;N,8.69;

Found:C69.54;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 whit 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 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 intermediat 3 gave, after recrystallisation from methanol,the title compound as white crystals m.p. : 157°C.
Analysis for $C_{25}H_{27}N_3O_3(0.5H_2O)$:
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 $C_{25}H_{27}N_3O_3$:
Calculat d: 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 $C_{25}H_{25}N_3O_3$ ($0.5H_2O$):

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 $C_{28}H_{25}N_3O_3$:

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 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 $C_{23}H_{23}N_3O_3$:
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[3,4-b]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 recrystallisation 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 $C_{21}H_{18}ClN_3O_2$ (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-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate[1] 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).

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 $C_{25}H_{25}N_3O_2$:
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 $C_{27}H_{29}N_3O_2$ ($0.25H_2O$):

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 $C_{28}H_{29}N_3O_2$ ($0.25\ H_2O$):

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

Analysis for $C_{25}H_{21}N_3O_2$ ($0.25H_2O$):

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 mp. : 292°C.
Analysis for $C_{19}H_{16}BrN_3O_2S$ ($0.25H_2O$):
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 $C_{20}H_{19}N_3O_2S$ ($0.25H_2O$):

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%.

Exampl 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 $C_{19}H_{17}N_3O_3$ ($0.5H_2O$):
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 $C_{20}H_{19}N_3O_3$ ($0.25H_2O$):
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 $C_{22}H_{21}N_3O_2$ ($0.25\ H_2O$):
Calculat d: 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 $C_{24}H_{25}N_3O_2$ ($0.5H_2O$):

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 $C_{25}H_{27}N_3O_2$ ($0.5H_2O$):

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 $C_{25}H_{25}N_3O_2$ ($1.1H_2O$):

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 $C_{25}H_{24}F_3N_3O_2$ ($0.5H_2O$):
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 $C_{22}H_{18}F_3N_3O_3$ ($0.5H_2O$):
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 r crystallisation from methanol, th title compound as yellow crystals m.p. :179-180°C.

Analysis for $C_{21}H_{19}N_3O_3(1.25H_2O)$:
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 $C_{22}H_{21}N_3O_4(0.25H_2O)$:
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 $C_{25}H_{24}N_4O_2$ ($1H_2O$):
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 $C_{25}H_{27}N_3O_2$ ($0.5H_2O$):

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%.

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, aft r recrystallisation from methanol, the title compound as white crystals m.p. : 182°C.

Analysis for $C_{24}H_{24}N_4O_4$ ($0.25H_2O$):
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.

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 N_2 for 16 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). After washing with water (3x20 mL), drying over Na_2SO_4 and evaporating to dryness, the residue was purified by flash chromatography eluting with CH_2Cl_2/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 $C_{22}H_{19}N_3O_4$:
Calculated:C,67.86;H,4.92;N,10.79;
Found:C,67.77;H,4.92;N,10.74%.
$[\alpha]_D^{20}$ = +71.0° (C=1.00; $CHCl_3$).

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 $C_{24}H_{23}N_3O_4$:
Calculated: C,69.05;H,5.55;N,10.07;
Found:C,69.06;H,5.49;N,10.12%.
$[\alpha]_D^{20}$ = +52.6° (C=1.14; $CHCl_3$).

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 $C_{25}H_{25}N_3O_4$:

Calculated: C,69.59;H,5.84;N,9.74;

Found:C,69.70;H,5.93;N,9.74%.

$[\alpha]_D^{20}$ = +50.2° (C=0.53; $CHCl_3$).

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 isobutylamine and intermediate 54 gave, after recrystallisation from methanol, the title compound as white crystals m.p. : 227-228°C.

Analysis for $C_{25}H_{25}N_3O_4$:

Calculated: C,69.59;H,5.84;N,9.74;

Found:C,69.52;H,5.87;N,9.74%.

$[\alpha]_D^{20}$ = +45° (C=1.04; $CHCl_3$).

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.

Analysis for $C_{26}H_{25}N_3O_4$:

Calculated: C,70.41;H,5.68;N,9.47;

Found:C,70.13.H,5.67.N,9.42%.

$[\alpha]_D^{20}$ = +36.6° (C=0.98; $CHCl_3$).

Example 83

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

The same two step procedure but starting from cyclohexylmethylamine 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 $C_{28}H_{29}N_3O_4$:

Calculated: C,71.32;H,6.20;N,8.91;

Found:C,71.30;H,6.29;N,8.74%.

$[\alpha]_D^{20}$ = +40.0° (C=0.99; $CHCl_3$).

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 $C_{25}H_{25}N_3O_3(0.5H_2O)$:

Calculated: C,70.74;H,6.17;N,9.90;

Found:C,70.98;H,6.09;N,9.92%.

$[\alpha]_D^{20}$ = +54.1° (C=1.03; $CHCl_3$).

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 buylamine and intermediate 57 gave, after recrystallisation from 2-propanol, the title compound as white crystals m.p. : 183-184°C.

Analysis for $C_{25}H_{27}N_3O_3(0.5H_2O)$:

Calculated: C,70.40;H,6.62;N,9.85;

Found:C,70.55;H,6.64;N,9.92%.

$[\alpha]_D^{20}$ = +45.4° (C=1.04; $CHCl_3$).

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 $C_{26}H_{27}N_3O_3$:

Calculated: C,72.71;H,6.34;N,9.78;

Found:C,72.53;H,6.39;N,9.53%.

$[\alpha]_D^{20}$ = +29.8° (C=1.07; $CHCl_3$).

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.

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° (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%.

$[\alpha]_D^{20}$ = +27.6° (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.Cl8.33.N,10.02%.

$[\alpha]_D^{20}$ = +61.3° (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° (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 titl 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° (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 recrystallisation 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° (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° (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 $C_{27}H_{27}N_3O_2$ ($0.25H_2O$):
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° (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]pyrido[3,4-b]indole-1,4-dione
To a stirred suspension of Intermediate 73 (12.5g) in MeOH (400ml) was add d at room temperature a solution of methylamine (33% in EtOH) (13.7ml) 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 (3 x 500ml), 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 (7.5g).
mp : 298-300°C.
$[\alpha]_D^{20}$ = + 71.3° (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 $C_{23}H_{21}N_3O_4$ ($0.4H_2O$):
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° (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 $SnCl_2.H_2O$ (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 (2 x 150 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 µL) and acetyl chloride (39 µL) and the resulting solution was stirred at room temperature for 2 hours. Aft r vaporation of THF, the resulting r sidue was taken up in CH_2Cl_2 (100 mL), washed with water (2 x 50 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 µL) and methanesulfonyl chloride (126 µL) 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 %.

$[\alpha]^{20°}_D$ = + 88° (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 %.
$[\alpha]^{20°}_D$ = + 51.7° (c = 0.49 ; $CHCl_3$).

Example 103
(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-methylendioxybenzyl)-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 intermediat 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.
$[\alpha]^{20°}_D$ = + 43° (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 %.
$[\alpha]^{20°}_D$ = + 38.3° (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 %.
$[\alpha]^{20°}_D$ = + 58.1° (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 %.
$[\alpha]^{20°}_D$ = + 70.4° (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 %.
$[\alpha]^{20°}_D$ = + 59° (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 %.

$[\alpha]^{20°}_D$ = + 52° (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]oxazinyl))-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 $C_{24}H_{24}N_4O_3$ (0.5 H_2O) :

Calculated : C, 67.75 ; H, 5.92 ; N, 13.17 ;

Found : C, 68.02 ; H, 6.00 ; N, 13.18 %.

$[\alpha]^{20°}_D$ = + 71.7° (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 %.

$[\alpha]^{20°}_D$ = + 20.4° (c = 0.5, $CHCl_3$).

Example 111

(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(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 $C_{23}H_{22}N_4O_2$ (0.5 H_2O) :

Calculated : C, 69.86 ; H, 5.86 ; N, 14.17 ;

Found : C, 70.13 ; H, 5.77 ; N, 14.06 %.

$[\alpha]^{20°}_D$ = + 55.9° (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 $C_{23}H_{23}N_3O_2$ (O.25 H_2O) :

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 %.

$[\alpha]^{20°}_D$ = + 97.7° (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 %.
$[\alpha]^{20°}_D$ = + 21.7° (c = 0.64, $CHCl_3$).

Example 115
(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

A solution of intermediate 81 (0.8 g, 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 %.
$[\alpha]^{20°}_D$ = + 106.8° (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 (2 x 20 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%.
$[\alpha]^{20°}_D$ = + 89.6° (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%.
$[\alpha]^{20°}_D$ = + 65.2° (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 hydrogenat d in the presence of 10 % Pd-C (75 mg) for 24 h at room temperature. After removal of the catalyst, the solvent was vaporated in

vacuo to leave a white solid which was recrystallisated 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 %.
$[\alpha]^{20°}_D$ = + 58.4° (c = 1.04 ; pyridine).

Example 119
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(5-(2-methylisoindolinyl))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 %.
$[\alpha]^{20°}_D$ = + 61.1° (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 pyrollidone	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 pyrollidone, 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 20mg/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.

CAPSULES

1.	mg/capsule
Active ingredient	50.0
Lactose	148.5
Polyvinyl pyrollidone	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
Crospovidone	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	50.0
Labrafil M1944CS	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 W lls at al. (Wells, J. N., Baird, C. E., Wu, Y. J.

and Hardman, J. G., Biochim. Biophys. Acta 384, 430 (1975)). The reaction medium contained 50mM Tris-HCl,pH 7.5, 5mM Mg-acetate, 250µg/ml 5'-Nucleotidase, 1mM EGTA and 0.15µM 8-[H^3]-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 IC_{50} values for the compounds examined were determined from concentration-response curves using typically concentrations ranging from 10nM to 10µM. 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 10th and 25th passage at confluence in 24-well culture dishes. Culture media was aspirated and replaced with PBS (0.5ml) 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 (0.25ml). The two ethanolic extracts were pool d 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 IC_{50} value of less than 500nM, and an EC_{50} 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 table 2 were studied in conscious spontaneously hypertensive rats (SHR). The compounds were administered orally at a dose of 5mg/kg in a mixture of 5% DMF and 95% olive oil. Blood pressure was measured from a catheter inserted in the carotid artery and recorded for 5 hours after administration. The results are expressed as Area Under the Curve (AUC from 0 to 5 hours, mmHg.hour) of the fall in blood pressure over time.

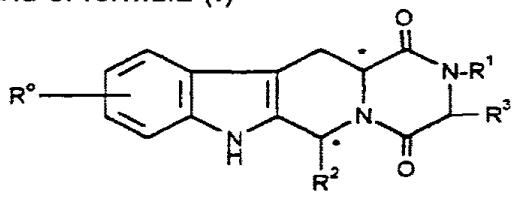
In Vivo Results

Example No.	AUC PO (mmHg.h)
36	99
63	95
79	171
82	111
84	77
89	117

Example No.	AUC PO (mmHg.h)
95	135
101	136

CLAIMS

1. A compound of formula (I)

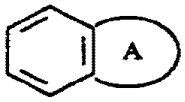


(I)

and salts and solvates thereof, in which:

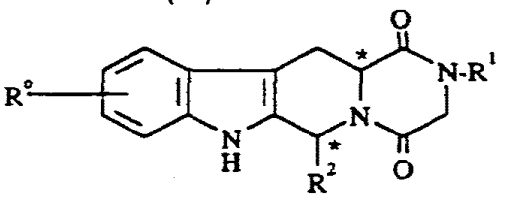
R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 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

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

2. A compound of formula (Ia)

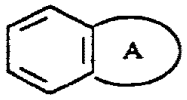


(Ia)

and salts and solvates thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl; and

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring 

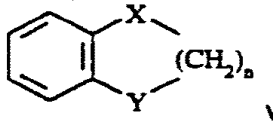
attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen.

3. A compound according to Claim 1 or 2, wherein R^o represents hydrogen.

4. A compound according to any of Claims 1 to 3, wherein R^1 represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylmethyl, pyridylC_{1-3}alkyl, furylC_{1-3}alkyl or optionally substituted benzyl.

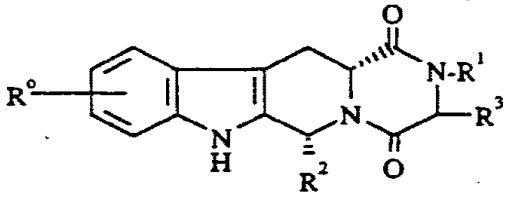
5. A compound according to any of Claims 1 to 3, wherein R^1 and R^3 together represent a 3-membered alkyl chain.

6. A compound according to any of Claims 1 to 4, wherein R^3 represents hydrogen.

7. A compound according to any of Claims 1 to 6, wherein R^2 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 CH_2 or O.

8. A cis isomer of formula (I) represented by formula (Ib)



(Ib)

and mixtures thereof with its cis optical enantiomer, including racemic mixtures, and salts and solvates of these compounds in which R^o is hydrogen or halogen and R^1, R^2 and R^3 are as defined in any preceding claim.

9. 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;
(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)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
and physiologically acceptable salts and solvates thereof.

10. (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 thereof.

11. A compound according to any of Claims 1 to 10, for use in the treatment of stable, unstable and variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood 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.

12. Use of a compound according to any of Claims 1 to 10, for the manufacture of a medicament for the treatment of stable, unstable and variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood 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.

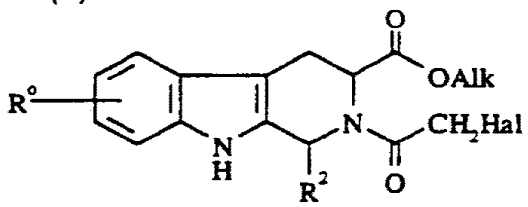
13. A method of treating stable, unstable and variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, vascular disorders, inflammatory 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 to any of Claims 1 to 10.

14. A pharmaceutical composition comprising a compound of the according to any of Claims 1 to 10, together with a pharmaceutically acceptable diluent or carrier therefor.

15. A process of preparing a pharmaceutical composition comprising a compound according to any of Claims 1 to 10, which process comprises mixing said compound together with a pharmaceutically acceptable diluent or carrier therefor.

16. A process of preparing a compound of formula (I), which process comprises:

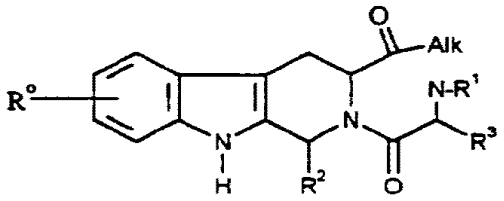
a process (A) for preparing a compound of formula (I), wherein R^3 represents hydrogen which process (A) comprises treating a compound of formula (II)



(II)

in which Alk represents C_{1-6}alkyl and Hal is a halogen atom, with a primary amine R^1NH_2; or

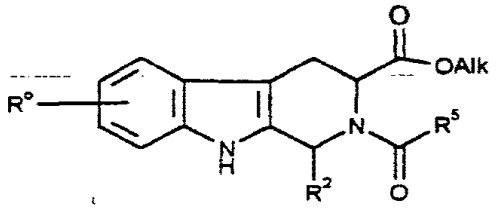
a process (B) for preparing a compound of formula (I), wherein R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain, which process (B) comprises cyclisation of a compound of formula (VIII)



(VIII)

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

a process (C) for preparing a compound of formula (I) wherein R^3 represents C_{1-3}alkyl, which process (C) comprises cyclisation of a compound of formula (X)



(X)

wherein Alk represents C_{1-6}alkyl and R^5 represents C_{2-5}alkyl, substituted at C_1 by a halogen atom; or

process (A), (B) or (C) as hereinbefore described followed by

i) an interconversion step; and/or either
ii) salt formation; or
iii) solvate formation.

17. Compounds of formulae (II), (III), (V), (VI), (VII), (VIII) and (X), with the exception for compounds (III), (V), (VI) and (VII) wherein R° is hydrogen, R^2 is phenyl and Alk is methyl.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 95/00183

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/14 A61K31/395 C07D471/04 C07D209/14
//(C07D471/14,241:00,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 917 599 (SAXENA ET AL.) 4 November 1975 see column 2, line 1-30 - column 9, line 1-40 ---	1
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 16,no. 5, 1973 pages 560-564, SAXENA ET AL. 'Agents Acting on the Central Nervous System.15. 2_Substituted 1,2,3,4,6,7,12,12a-octahydropyrazino[2',1':6,1]pyrido[3,4-b]indoles. A New Class of Central Nervous System Depressants' see page 561, column 1 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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Date of the actual completion of the international search	Date of mailing of the international search report
24 May 1995	16. 06. 95

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Interr nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEM. PHARM. BULL., vol. 33,no. 8, 1985 pages 3237-3249, ISHIDA; NAKAMURA; IRIE; OHISHI 'A New Method for the preparation of 3,4-Dihydro- and 1,2,3,4-Tetrahydro-beta-carbolines' see page 3237 -----	17

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-3917599	04-11-75	AU-A-	6164973	24-04-75
		CH-A-	596205	15-03-78
		FR-A,B	2223013	25-10-74
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(71) Applicant *(for all designated States except US)*: LABORATOIRE GLAXO WELLCOME S.A. [FR/FR]; 43, rue Vineuse, F-75116 Paris (FR).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: DAUGAN, Alain, Claude-Marie [FR/FR]; Laboratoire Glaxo Wellcome S.A., Centre de Recherches, Z.A. de Courtaboeuf, 25, avenue de Quebec, F-91940 Les Ulis (FR).

(74) Agents: FILLER, Wendy, Anne et al.; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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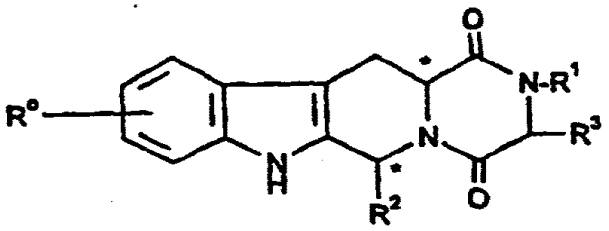
(54) Title: USE OF CGMP-PHOSPHODIESTERASE INHIBITORS TO TREAT IMPOTENCE

(57) Abstract

The use of compounds of formula (I) (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, (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, and physiologically acceptable salts and solvates thereof, in the treatment of impotence.



(I)

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USE OF CGMP-PHOSPHODIESTERASE INHIBITORS TO TREAT IMPOTENCE

This invention relates to the use of tetracyclic derivatives which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) in the treatment of impotence.

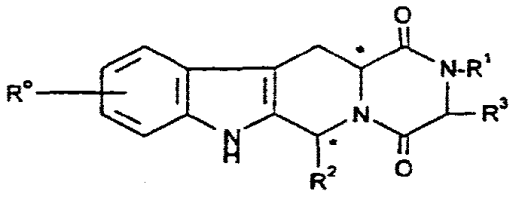
Impotence can be defined as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age.

Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c. injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E_1, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodi sterases (cGMP PDEs). GB 9514464.8, which is the priority document for the present application describes the syntheses of the compounds of the invention and their utility in impotence. WO95/19978, which

was unpublished at the priority date of the present application, also describes the syntheses of the compounds of the invention and their utility in other diseases associated with inhibition of cGMP PDEs. The compounds may be represented by the following general formula (I):

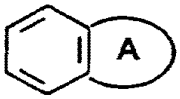


(I)

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

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 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

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

Suitable individual compounds of the invention for use in the treatment of erectile dysfunction 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[3,4-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;
(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)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
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;
(3S, 6R,12aR)-2,3,6,7,12,12a-hexahydro-3-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.

The specific compounds of the invention are:

(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 (Compound A); and

(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 (Compound B);

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

Unexpectedly, it has now been found that compounds of formula (I), and in particular compounds A and B, are useful in the treatment of erectile dysfunction. Furthermore the compounds may be administered orally, thereby

obviating the disadvantages associated with i.c. administration. Thus the present invention concerns the use of compounds of formula (I), and in particular compounds A and B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

The pharmaceutically acceptable salts of the compounds of formula (I), and in particular compounds A and B 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, benzenesulphonate and p-toluenesulphonate salts. Compounds of formula (I), and in particular compounds A and B can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

It has been shown that compounds of the present invention are potent and selective inhibitors of cGMP specific PDE. It has now been surprisingly found that human corpus cavernosum contains three distinct PDE enzymes. Th predominant PDE has further surprisingly been found to be cGMP PDE. As a consequence of the selective PDE V inhibition exhibited by compounds of the present invention, the subject compounds can elevate cGMP levels, which in turn can mediate relaxation of the corpus cavernosum tissue and consequent penile erection.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For administration to man in the curative or prophylactic treatment of the disorders identified above, oral dosages of a compound of formula (I), and in particular compounds A and B will generally be in the range of from 0.5-800mg daily for an average adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400mg 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 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, compounds of formula (I), and in particular compounds A and B 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 caprylic/capric glycerides).

For veterinary use, a compound of formula (I), and in particular compound A or B or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular male animal.

Thus the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

There is further provided a process for the preparation of a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

Moreover, the invention includes the use of a compound of formula (I), and in particular compound A or B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

A compound of formula (I), and in particular compound A or B, may also b used in combination with other therapeutic agents which may be useful in the treatment of erectile dysfunction substantially as hereinbefore described. The invention thus provides, in another aspect, a combination of a compound of formula (I), and in particular compound A or B together with another therapeutically active agent.

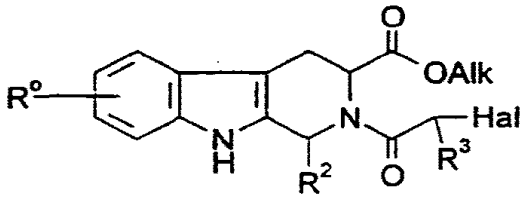
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

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 the invention will be readily appreciated by those skilled in the art.

The compounds of the invention may be prepared by any suitable method known in the art or by the following process which forms part of the present invention. The process has been previously substantially described in the priority document of the present invention GB9514464.8, and in WO95/19978.

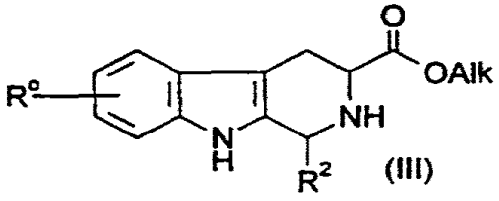
Thus, a process for preparing a compound of formula (I) comprises treating a compound of formula (II)



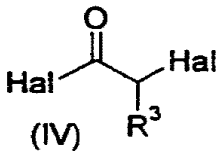
(II)

(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°C to reflux (e.g. at about 50°C).

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



(III)



(IV)

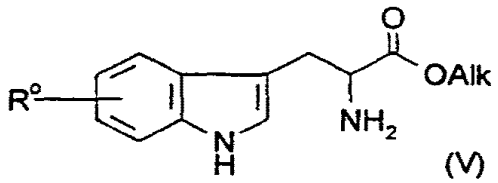
in a suitable solvent such as a halogenated hydrocarbon (e.g. trichloromethane or dichloromethane), or an ether (e.g. tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g. a trialkylamine such as triethylamine) or an alkali metal carbonate or bicarbonate (e.g. $NaHCO_3$).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

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



(V)

(where Alk is as previously defined) or a salt thereof (e.g. the hydrochloride salt) with 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°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 chlorid at a temperature of from 0°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.

The pharmaceutically acceptable acid addition salts of a compound of formula (I), and in particular compound A or B 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 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 compound A or B 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.

The syntheses of compounds A and B and of the intermediates for use therein are illustrated by the following examples. The examples have been previously described in the priority document of the instant invention GB9514464.8, and the corresponding Intermediate or Example numbers therein are shown in parentheses next to the current Intermediate or Example number.

In the Examples section hereinafter the following abbreviations are used:

MeOH (methanol) and EtOH (ethanol),

Intermediate 1 (54)

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

To a stirred solution of D-tryptophan methyl ester (11 g) and piperonal (7.9 g) in anhydrous CH_2Cl_2 (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 CH_2Cl_2 (200 mL) and washed with a saturated aqueous solution of $NaHCO_3$, then with water (3x200 mL) and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure and the residue containing the two geometric isomers was purified by flash

chromatography eluting with dichloromethane/ethyl acetate (97/3) to give as the firsr eluting product the title compound (6.5 g)

m.p. : 154°C

Intermediate 2 (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. mol). Intermediate 1 (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.

Example 1 (78) (Compound A)

(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 1 (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.

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 N_2 for 16 hours. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). After washing with water (3x20 mL), drying over Na_2SO_4 and evaporating to dryness, the residue was purified by flash chromatography eluting with CH_2Cl_2/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 $C_{22}H_{19}N_3O_4$:

Calculated:C,67.86;H,4.92;N,10.79;

Found:C,67.77;H,4.92;N,10.74%.

$[\alpha]^{20°}_D$ = +71.0° (C=1.00; $CHCl_3$).

Example 2 (117) (Compound B)

(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 2 (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%.

$[\alpha]^{20°}_D$ = + 65.2° (c = 1.15 ; $CHCl_3$).

The following compound was similarly prepared:

Example 3

(3S, 6R,12aR)-2,3,6,7,12,12a-Hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione as white crystals using ammonia as the base.

m.p. : 319-321°C.

Analysis for $C_{22}H_{19}N_3O_4$:

Calculated : C, 67.86 ; H, 4.92 ; N, 10.79 ;

Found : C, 67.86; H, 5.17; N, 10.72%.

$[\alpha]^{20°}_D$ = + 107° (c = 1 ; pyridine).

Compounds A and B 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 pyrollidone	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 pyrollidone, 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 20mg/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.

CAPSULES

1.	mg/capsule
Active ingredient	50.0
Lactose	148.5
Polyvinyl pyrollidone	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

Crospovidone	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	50.0
Labrafil M1944CS	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.

Inhibitory effect on cGMP-PDE

cGMP-PDE activity of compounds of the present invention was measured using a one-step assay adapted from Wells at al. (Wells, J. N., Baird, C. E., Wu, Y. J. and Hardman, J. G., Biochim. Biophys. Acta 384, 430 (1975)). The reaction medium contained 50mM Tris-HCl,pH 7.5, 5mM Mg-acetate, 250µg/ml 5'-Nucleotidase, 1mM EGTA and 0.15µM 8-[H^3]-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 IC_{50} values for the compounds examined were determined from concentration-response curves using typically concentrations ranging from 10nM to 10µM. 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 10th and 25th passage at confluence in 24-well culture dishes. Culture media was aspirated and replaced with PBS (0.5ml) 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 (0.25ml). 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 IC_{50} value of less than 500nM, and an EC_{50} value of less than 5. In vitro test data for representative compounds of the invention is given in following Table 1:

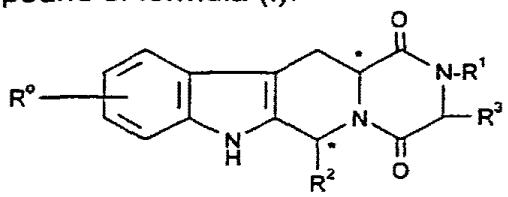
Table 1

Example No.	IC_{50} nM	EC_{50} μM
1	2	0.2
2	2	0.2

The above data demonstrates the ability of the subject compounds of the invention to inhibit cGMP PDE, and hence their utility in the treatment of erectile dysfunction substantially as hereinbefore described.

CLAIMS

1. Use of a compound of formula (I):

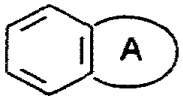


(I)

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

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 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

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain;

for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

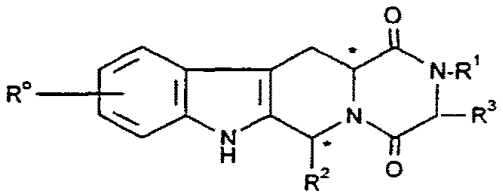
2. Use of a compound selected from

(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

(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;

and physiologically acceptable salts and solvates thereof for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

3. Method for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising administration of a compound of formula (I):



(I)

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

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 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

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

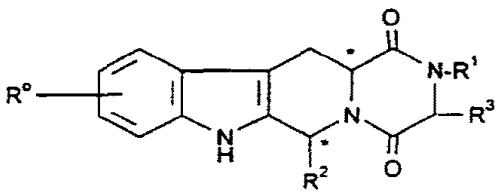
4. Method for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising administration of a compound selected from

(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-dion ; and

(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

and physiologically acceptable salts and solvates thereof.

5. A pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I):

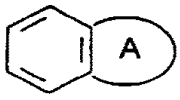


(I)

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

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 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

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain;

together with a pharmaceutically acceptable diluent or carrier.

6. A pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound s lected from

(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

(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

and physiologically acceptable salts and solvates thereof, together with a pharmaceutically acceptable diluent or carrier.

7. A process for the preparation of a pharmaceutical composition according to Claim 5 for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound of formula (I), and physiologically acceptable salts and solvates thereof, with a pharmaceutically acceptable diluent or carrier.

8. A process for the preparation of a pharmaceutical composition according to Claim 6 for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising formulating a compound selected from

(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

(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

and physiologically acceptable salts and solvates thereof, with a pharmaceutically acceptable diluent or carrier.

9. A method of treating a male animal, including man, to cure or prevent erectile dysfunction which comprises treating said male animal with an effective amount of a pharmaceutical composition according to Claim 5 or 6.

10. Use of a pharmaceutical composition according to Claim 5 or 6, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

11. A combination of a compound selected from

(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

(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

and physiologically acceptable salts and solvates thereof, together with another therapeutically active agent, for simultaneous, separate, or sequential use in the treatment of erectile dysfunction in a male animal, including man.

12. A pharmaceutical formulation comprising a combination according to Claim 11 together with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

Ir .tional Application No
PCT/EP 96/03024

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. UROL., vol. 152, no. 6 pt 1, 1994, pages 2159-2163, XP000604575 C. SPARWASSER ET AL.: "Smooth muscle tone regulation in rabbit cavernosal and spongiosal tissue by cyclic AMP- and cyclic GMP-dependent mechanisms." see the whole document ---	1-5,9-11
P,Y	WO,A,95 19978 (LABORATOIRES GLAXO SA) 27 July 1995 cited in the application see page 6 - page 7; claims	1-5,9-11
X	see page 71 - page 74 --- -/--	6-8,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 1996	29. 10. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Klaver, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/03024

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NEUROL. URODYN., vol. 13, no. 1, 1994, pages 71-80, XP000568165 F. TRIGO-ROCHA ET AL.: "Intracellular mechanism of penile erection in monkeys."	

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

It ational application No.
PCT/EP 96/03024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 3, 4, 9, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The phrase "...another therapeutically active agent..." is insufficienty specific.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/03024

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9519978	27-07-95	AU-A- 1574895	08-08-95
		CA-A- 2181377	27-07-95
		FI-A- 962927	19-07-96
		ZA-A- 9500424	27-09-95

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/415, 31/505

A1

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(21) International Application Number: PCT/US99/07046

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(30) Priority Data:

09/081,640	20 May 1998 (20.05.98)	US
09/082,977	21 May 1998 (21.05.98)	US
09/106,517	29 June 1998 (29.06.98)	US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications

US	09/081,640 (CIP)
Filed on	20 May 1998 (20.05.98)
US	09/082,977 (CIP)
Filed on	21 May 1998 (21.05.98)
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(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033–0530 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: ESTOK, Thomas, Mark [US/US]; 1515 Charlotte Road, Plainfield, NJ 07060 (US).

(74) Agents: MAJKA, Joseph, T. et al.; Schering–Plough Corporation, Patent Dept. K–6–1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033–0530 (US).

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(54) Title: COMBINATION OF PHENTOLAMINE AND CYCLIC GMP PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF SEXUAL DYSFUNCTION

(57) Abstract

A method of treating sexual dysfunction comprising administering a therapeutically effective amount of a combination of phentolamine and cGMP PDE inhibitor such as sildenafil, as well as pharmaceutical compositions and kits useful in those methods, are disclosed.

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COMBINATION OF PHENTOLAMINE AND CYCLIC GMP PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF SEXUAL DYSFUNCTION

BACKGROUND

The present invention relates to pharmaceutical compositions comprising a combination of phentolamine and cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE) inhibitors and to methods of treating sexual dysfunction, especially erectile dysfunction, comprising administering an effective amount of a combination of phentolamine and cGMP PDE inhibitors.

The use of the pharmaceutical compositions and methods of this invention results in an unexpected potentiation of human sexual response.

SUMMARY OF THE INVENTION

The present invention is directed to the use of phentolamine in combination with cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE) inhibitors for the treatment of human sexual dysfunction. Preferably, the invention contemplates the use of Type V cGMP PDE inhibitor in combination with phentolamine with sildenafil being the preferred Type V cGMP PDE inhibitor.

More particularly, the present invention relates to a method of treating sexual dysfunction, especially erectile dysfunction, comprising administering to a human in need of such treatment an effective amount of a combination of phentolamine, or a pharmaceutically acceptable salt, solvate or ester thereof, and a cGMP PDE inhibitor, or a pharmaceutically acceptable salt or solvate thereof. Preferably, the invention contemplates the use of Type V cGMP PDE inhibitor in combination with phentolamine, with sildenafil being the preferred Type V cGMP PDE inhibitor.

Phentolamine mesylate and sildenafil citrate are the most preferred active ingredients for use in the methods of this invention.

In a second aspect, the invention relates to a pharmaceutical composition comprising an effective amount of phentolamine, or a pharmaceutically acceptable salt, solvate or ester thereof, and a cGMP PDE inhibitor, or a pharmaceutically acceptable salt solvate thereof. Preferably, the pharmaceutical compositions envisioned by the present invention comprise phentolamine, or a pharmaceutically acceptable salt, solvate or ester thereof, and a Type V cGMP PDE inhibitor, or a pharmaceutically acceptable salt solvate thereof, with sildenafil being the preferred Type V cGMP PDE inhibitor. Phentolamine mesylate and sildenafil citrate are the most preferred active ingredients of the pharmaceutical compositions of this invention.

In a third aspect, the invention relates to a kit comprising in one container an effective amount of phentolamine, or a pharmaceutically acceptable salt, solvate or ester thereof in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt, solvate thereof in a pharmaceutically acceptable carrier, with sildenafil being the preferred Type V cGMP PDE inhibitor. Phentolamine mesylate and sildenafil citrate are the most preferred active ingredients for use in the kits of this invention.

In a fourth aspect, the invention relates to a pharmaceutical composition for the treatment of human sexual dysfunction comprising a therapeutically effective amount of a first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a second vasodilating agent or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. Preferably, the first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is an adrenergic blocker. More preferably, the adrenergic blocker is an alpha-adrenergic blocker. Also preferred is that the alpha adrenergic blocker is selected from the group consisting of an alpha1-adrenergic blocker, an alpha2-adrenergic blocker or both an alpha1-adrenergic blocker and an alpha2-adrenergic blocker. Preferably, the second vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is a cGMP PDE inhibitor. Also preferrred is that the first vasodilating agent or a pharmaceutically acceptable salt or solvate or

ester thereof is an adrenergic blocker and the second vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is a cGMP PDE inhibitor. The adrenergic blocker can be selected from the group consisting of phentolamine, phentolamine mesylate, phentolamine hydrochloride, phenoxybenazmine, tolazoline, dibenamine, yohimbine, terazosin, doxazosin, prazosin and the like. The cGMP PDE inhibitor can a cGMP PDE V inhibitor. Preferably, the cGMP PDE V inhibitor is selected from the group consisting of:
sildenafil,
(6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrizino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound A), and
(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 (Compound B) or a pharmaceutically acceptable salt or solvate thereof.

In a fifth aspect, the invention relates to a method of treating human sexual dysfunction comprising the simultaneous or sequential administration of a therapeutically effective amount of a therapeutically effective amount of a first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a second vasodilating agent or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. The classes and types of compounds which can be used in the method are described in the fourth aspect, above.

DETAILED DESCRIPTION

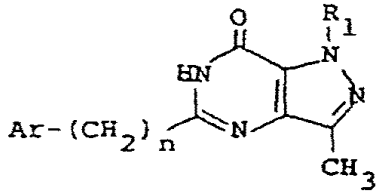
Humans include, of course, males and females. Although the pharmaceutical compositions of the present invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction. Such female sexual dysfunction may include orgasmic dysfunction due to clitoral irregularities or disturbances.

Phentolamine, 3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl)amino]phenol, and pharmaceutically acceptable salts, solvates, hydrates, crystalline polymorph forms and the free base thereof,

are useful in the treatment of sexual dysfunction. A rapidly disintegrating tablet and method of use to treat sexual dysfunction is disclosed in United States Patent No. 5,731,339, also incorporated herein by reference. Representative formulations comprising phentolamine are disclosed in U.S. 5,731,339. Phentolamine can exist in unsolvated as well as solvated forms, including hydrated forms, e.g. hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention. Phentolamine can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrohalic acids such as hydrochloric and hydrobromic; as well as other acids such as sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, toluenesulfonic and other mineral and carboxylic acids known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base form for purposes of this invention. Phentolamine can also form crystalline polymorph forms or crystalline forms thereof using suitable or conventional crystallization procedures.

The present invention is directed to the use of cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE) inhibitors in combination with the salts or esters of phentolamine, preferably, with phentolamine mesylate for the treatment of human sexual dysfunction, preferably erectial dysfunction Examples of cGMP PDE inhibitors contemplated in this invention are as follows and are described in the following documents, as indicated. The disclosure of each of the below-referred to document is incorporated herein by reference.

European published application number 0201188, which discloses compounds of the formula



(I)

and the pharmaceutically acceptable salts thereof, in which:

R_1 is a lower alkyl of from one to six carbon atoms, a lower alkenyl of from one to six carbon atoms, a lower hydroxyalkyl of from one to six carbon atoms, a lower hydroxyalkenyl of from two to six carbon atoms, a lower aminoalkyl of from one to six carbon atoms, or a lower aminoalkenyl of from two to six carbon atoms;

n is 0 or an integer of from 1 to 4; and

Ar is a radical of the following general formula (R_2)

or 2, 3, or 4-pyridyl, in which X, Y, and Z are, independently, (1) hydrogen; (2) lower alkyl of from one to six carbon atoms; (3) halogen, (4) hydroxyl; (5) lower alkoxy of from one to six carbon atoms; (6) nitro; (7) amino; (8) NR'R" wherein R' and R" are each, independently, (a) hydrogen or (b) lower alkyl of from one to six carbon atoms optionally substituted by (i) amino, (ii) morpholino or (iii) cycloalkyl of from five to seven carbon atoms; (9) sulfonyl; or

(10)-$SO_2NR'R"$ wherein R' and R" are as defined above;

with the proviso that not all of X, Y, and Z can be nitro, amino, or NR'R" at once.

Preferred compounds include:

1-ethyl-3-methyl-5-phenylpyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-phenylpyrazolo[4,3-d]pyrimidine-7-one;

1,3-dimethyl-5-(4-chlorophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(4-methylphenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(4-nitrophenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(4-trifluoromethylphenyl)pyrazolo-[4,3-d]-pyrimidine;

1,3-dimethyl-5-(4-aminophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(3-aminophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(3-nitrophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(2-methoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(3,4-dichlorophenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(3,4-dimethoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(2,4-dimethoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(2-nitro-4-chlorophenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(2-amino-4-chlorophenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

1,3-dimethyl-5-(4-sulfonic acid phenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

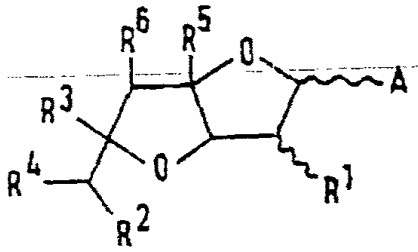
1,3-dimethyl-5-[4-(N-2-(dimethylamino)ethyl)-benzenesulfonamide]pyrazolo[4,3-d]pyrimidine-7-one;

1,3-dimethyl-5-(3,5-dimethoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one; or

1,3-dimethyl-5-(3-methoxyphenyl)pyrazolo[4,3-d]-pyrimidine-7-one.

PNSDOCID: <WO 9959584A1_I_>

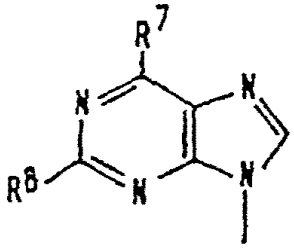
European published application number 0214708, which discloses compounds of the formula

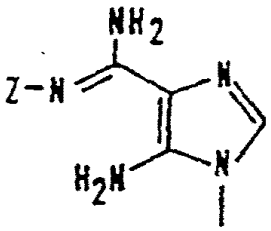


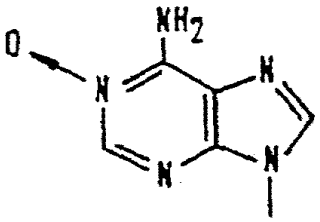
(I)

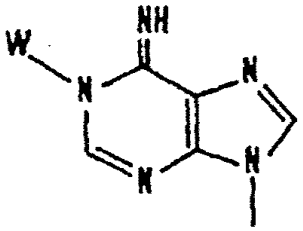
in which:

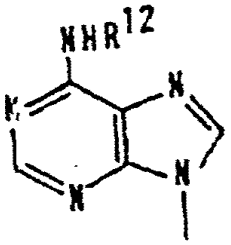
A represents a group of formula:

(a) 

(b) 

(c) 

(d) 

or (e)  ;

R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom or a group of formula $-OR^4$;

R^3 and R^4 are the same or different and each represents a carbamoyl group or a carboxy group;

R^5 and R^6 both represent hydrogen atoms or together they represent an extra carbon-carbon bond between the carbon atoms to which they are attached;

R^7 represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$, $-NR^{10}R^{11}$ or $-SR^9$;

R^8 represents a halogen atom or a group of formula $-OR^9$, $-NR^{10}R^{11}$ or $-SR^9$;

R^9 represents a hydrogen atom, a C_1-C_4 alkyl group, an alkylsulphonyl group, a haloalkylsulphonyl group, an arylsulphonyl group or a hydroxy-protecting group;

R^{10} and R^{11} are the same or different and each represents a hydrogen atom, a hydroxy group, a C_1-C_4 alkyl group, a C_1-C_4 hydroxyalkyl group, a C_1-C_4 aminoalkyl group, an aralkyl group, an aryl group, a C_1-C_4 alkoxy group, an aralkyloxy group, an amino group, a C_1-C_{20} aliphatic acyl group or an aromatic acyl group; or R^{10} and R^{11} together represent a substituted methylene group, or R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a heterocyclic group having 5 or 6 ring atoms, of which, in addition to the nitrogen atom shown, 0 or 1 are additional oxygen, nitrogen or sulphur hetero-atoms, said heterocyclic group being unsubstituted or having from 1 to 3 C_1-C_4 alkyl and/or C_1-C_4 alkoxy substituents;

R^{12} represents a C_1-C_4 alkyl group;

Z represents a hydrogen atom, a hydroxy group or a substituted hydroxy group; and

W represents an alkoxy group or an aralkoxy group;

provided that, when A represents said group of formula (e), R^5 and R^6 both represent hydrogen atoms;

and pharmaceutically acceptable salts and esters thereof.

Preferred compounds include:

2-Amino-6-desamino-6-hydroxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxygriseolic acid 7'-amide and pharmaceutically acceptable salts and esters thereof.

2-Aminogriseolic acid and pharmaceutically acceptable salts and esters thereof.

Bis(pivaloyloxymethyl) 2-amino-6-desamino-6-hydroxygriseolate and pharmaceutically acceptable salts thereof.

2-Amino-N 4'-methoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-N4'-benzyloxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Fluorogriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Chlorogriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Chloro-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-2'-chloro-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-2'-chloro-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Chloro-2'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

Griseolic acid N1-oxide and pharmaceutically acceptable salts thereof.

2-Acetylamino-6-desamino-6-hydroxy-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

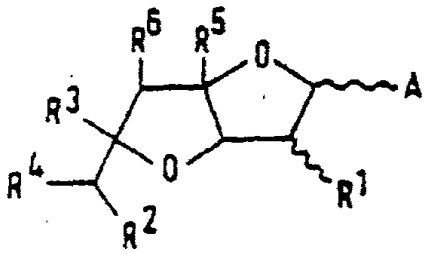
2-Acetylamino-6-desamino-6-hydroxy-4',5'-dihydro-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-6-desamino-6-hydroxy-4',5'-dihydro-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2,6-Dichloro-6-desamino-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

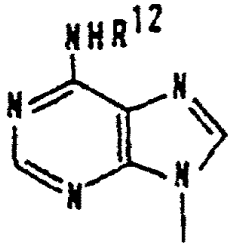
2-Chloro-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

European published application number 0319050, which discloses compounds of the formula



(I)

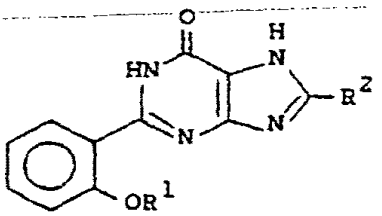
in which:
A represents a group of formula:



;

R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom or a group of formula $-OR^8$;
R^3 and R^4 are the same or different and each represents a carbamoyl group or a carboxy group;
R^5 and R^6 both represent hydrogen atoms;
R^8 represents a hydrogen atom, a C_1-C_6 alkyl group, an alkylsulphonyl group, a haloalkylsulphonyl group, an arylsulphonyl group or a hydroxy-protecting group;
R^{12} represents a C_1-C_6 alkyl group;
and pharmaceutically acceptable salts and esters thereof.

European published application number 0293063, which discloses compounds of the formula



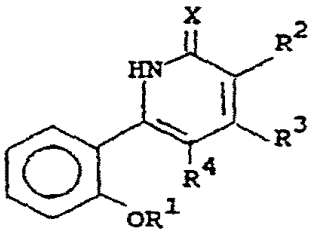
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl or C_{2-6}alkenyl, and
R^2 is hydrogen or hydroxy.

Preferred compounds include:

2-(2-propoxyphenyl)-6-purinone,
2-(2-ethoxyphenyl)-6-purinone,
2-(2-butoxyphenyl)-6-purinone,
2-(2-isobutoxyphenyl)-6-purinone,
2-(2-propoxyphenyl)purine-6,8-dione,
2-(2-methoxyphenyl)purine-6,8-dione,
2-(2-ethoxyphenyl)purine-6,8-dione,
2-(2-butoxyphenyl)purine-6,8-dione,
2-(2-isobutoxypheny)purine-6,8-dione, or
2-(2-allyloxyphenyl)purine-6-8-dione
or a pharmaceutically acceptable salt thereof.

European published application number 0347027, which discloses compounds of the formula



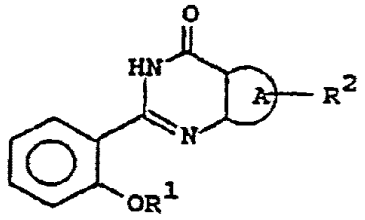
(1)

or a pharmaceutically acceptable salt thereof, wherein
X is O or S;
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, or C_{1-4}alkyl substituted by 1 to 6 fluoro groups;
R^2 is hydrogen, -CN, $-CONR^5R^6$, $-CO_2R^7$, 5-tetrazolyl, $-NO_2$, $-NH_2$ or $-NHCOR^8$ wherein R^5, R^6, R^7 and R^8 are independently hydrogen or C_{1-4}alkyl;
R^3 is hydrogen or C_{1-4}alkyl; and
R^4 is hydrogen or C_{1-4}alkyl;
with the proviso that R^1 is not methyl when R^2 is $-CO_2H$, $-CO_2CH_2CH_3$ or -CN, X is O, R^3 is hydrogen and R^4 is hydrogen or methyl.

Preferred compounds include:

3-cyano-6-(2-propoxyphenyl)-2(1H)-pyridinone,
6-(2-propoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(2-propoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxylic acid,
methyl 6-(2-propoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxylate,
6-(2-propoxyphenyl)-3-(1H-tetrazol-5-yl)-2(1H)-pyridinone,
6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-nitro-6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-6-(2-ethoxyphenyl)-2(1H)-pyridinone ,
3-amino-6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-4-methyl-6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-5-methyl-6-(2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-6-(2-(1,1,2,3,3,3-hexafluoropropoxy)phenyl-2(1H)-pyridinone,
3-cyano-6-(2-propoxyphenyl)-2(1H)-pyridinethione,
1,2-dihydro-4-methyl-2-oxo-6-(2-propoxyphenyl)pyridine-3-carboxylic acid,
methyl 1,2-dihydro-4-methyl-2-oxo-6-(2-propoxyphenyl)-pyridine-3-carboxylate,
1,2-dihydro-4-methyl-2-oxo-6-(2-propoxyphenyl)pyridine-3-carboxamide,
3-cyano-6-(2-cyclopropylmethoxyphenyl)-2(1H)-pyridinone,
6-(2-butoxyphenyl)-3-cyano-2(1H)-pyridinone,
6-(2-allyloxyphenyl)-3-cyano-2(1H)-pyridinone,
3-cyano-6-[2-(2-methylpropoxy)phenyl]-2(1H)-pyridinone,
6-(2-ethoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(2-cyclopropylmethoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(2-butoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(2-allyloxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide, or
6-[2-(2-methylpropoxyphenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
or a pharmaceutically acceptable salt thereof.

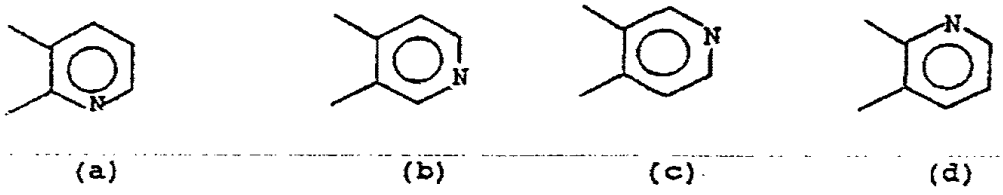
European published application number 0347146, which discloses compounds of the formula



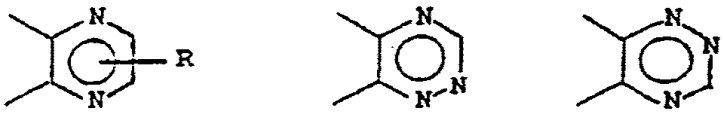
(1)

or a pharmaceutically acceptable salt thereof, wherein

is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g) :



(a) (b) (c) (d)



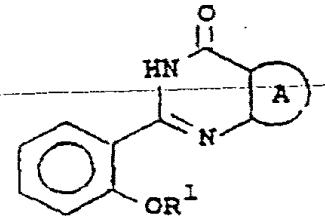
(e) (f) (g),

R^1 is C_1-$_6$alkyl, C_2-$_6$alkenyl, C_3-$_5$cycloalkylC_1-$_6$alkyl, or C_1-$_6$alkyl substituted by 1 to 6 fluoro groups;
R^2 is C_1-$_6$alkylthio, C_1-$_6$alkylsulphonyl, C_1-$_6$alkoxy, hydroxy, hydrogen, hydrazino, C_1-$_6$alkyl, phenyl, -NHCOR^3 wherein R^3 is hydrogen or C_1-$_6$alkyl, or -NR^{4}R^5 wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_3-$_5$cycloalkyl or C_1-$_6$alkyl which is optionally substituted by -CF_3, phenyl, -S(O)$_n$C$_1$-$_6$alkyl wherein n is 0, 1 or 2, -OR^6, -CO_2R^7 or -NR^{8}R^9 wherein R^6 to R^9 are independently hydrogen or C_1-$_6$alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -S(O)$_n$C$_1$-$_6$alkyl, -OR^6 or -NR^{8}R^9 groups; and
R is hydrogen and can also be hydroxy when R^2 is hydroxy.

Preferred compounds include:

2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,4-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[4,3-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pyrido[3,2-d]pyrimid-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4(3H)-one,
2-(2-propoxyphenyl)pteridin-4,6(3H,5H)-dione,
2-(2-propoxyphenyl)pteridin-4,6,7(3H,5H,8H)-trione,
5,6-dihydro-3-methylthio-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e] [1,2,4]triazine,
3-amino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylamino-5,6-dihydro-5-oxo-7-(2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methoxy-5,6-dihydro-5-oxo-7-)2-propoxyphenyl)pyrimido[5,4-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-amino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methoxy-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3,8-dioxo-6-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine,
3-dimethylamino-8-oxo-6-(2-propoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-allyloxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-isobutoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine,
3-methylthio-8-oxo-6-(2-cyclopropylmethoxyphenyl)-7,8dihydropyrimido[4,5-e][1,2,4]triazine or
3-methylthio-8-oxo-6-(2-methoxyphenyl)-7,8-dihydropyrimido[4,5-e][1,2,4]triazine
or a pharmaceutically acceptable salt thereof.

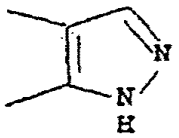
European published application number 0349239, which discloses compounds of the formula



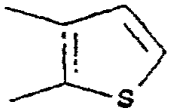
(1)

or a pharmaceutically acceptable salt thereof, wherein

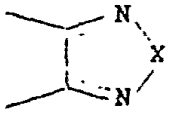
is a ring of sub-formula (a), (b) or (c):



(a)



(b)



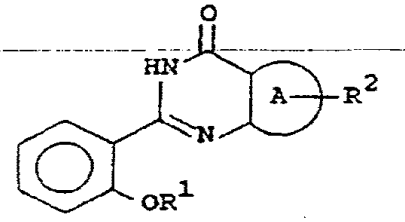
(c),

X is oxygen or sulphur, and
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups.

Preferred compounds include:

6-(2-propoxyphenyl)pyrazolo[3,4-d]pyrimidin-4(5H)-one,
2-(2-propoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one,
2-(2-propoxyphenyl)[1,2,5]oxadiazolo[3,4-d]pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)[1,2,5]thiadiazolo[3,4-d]pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

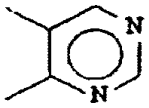
European published application number 0351058, which discloses compounds of the formula



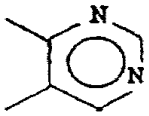
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_1-_6alkyl, C_2-_6alkenyl, C_3-_5cycloalkylC_1-_6alkyl, or C_1-_6alkyl substituted by 1 to 6 fluoro groups;
R^2 is C_1-_6alkylthio, C_1-_6alkylsulphonyl, C_1-_6alkoxy, hydroxy, hydrogen, hydrazino, C_1-_6alkyl, phenyl, $-NHCOR^3$ wherein R^3 is hydrogen or C_1-_6alkyl, or $-NR^4R^5$, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_3-_5cycloalkyl or C_1-_6alkyl which is optionally substituted by $-CF_3$, phenyl, $-S(O)_nC_1-_6$alkyl wherein n is 0, 1 or 2, $-OR^6$, $-CO_2R^7$ or $-NR^8R^9$ wherein R^6 to R^9 are independently hydrogen or C_1-_6alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said $-S(O)_nC_1-_6$alkyl, $-OR^6$ or $-NR^8R^9$ groups; and

is a ring of sub-formula (a) or (b) :



(a)



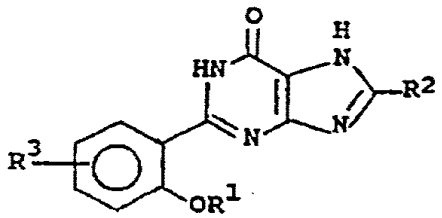
(b).

Preferred compounds include:

7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-ethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-isobutoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-cyclopropylmethoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylthio-2-(2-allyloxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-amino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-dimethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-hydrazino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-ethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-ethyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine
7-methylamino-2-(2-methoxyphenyl)-4-oxo-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-phenyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,

7-morpholino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-cyclopropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-acetamido-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-propylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(3-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-methoxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-dimethylaminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-hydroxypropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(3-methylthiopropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-aminoethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine hydrochloride,
7-(3-methylsulphinylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(3-methylsulphonylpropylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
4,7-dioxo-2-(2-propoxyphenyl)-3,4,7,8-tetrahydropyrimido[4,5-d]pyrimidine,
7-methylsulphonyl-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-diethylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-ethoxycarbonylethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(ethoxycarbonylmethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-carboxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(carboxymethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-ethoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-methoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2,2,2-trifluoroethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-propoxy-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(N-ethyl-N-hydroxyethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-dipropylamino-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine,
7-(2-phenethylamino)-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine, or
4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[5,4-d]pyrimidine,
or a pharmaceutically acceptable salt thereof.

European published application number 0352960, which discloses compounds of the formula



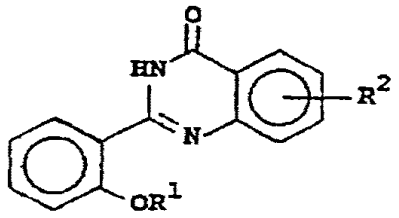
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, phenylC_{1-4}alkyl or C_{1-4}alkyl substituted by 1 to 6 fluoro groups;
R^2 is hydrogen, hydroxy, C_{1-4}alkyl, phenyl, mercapto, C_{1-4}alkylthio, CF_3 or amino;
R^3 is hydrogen, nitro, amino, C_{1-4}alkanoylamino, C_{1-4}alkoxy, C_{1-4}alkyl, halo, $SO_2NR^4R^5$, $CONR^4R^5$, cyano or C_{1-4}alkylS(O)n;
R^4 and R^5 are independently hydrogen or C_{1-4}alkyl; and
n is 0, 1 or 2;
provided that R^3 is not hydrogen when R^1 is C_{1-6}alkyl or C_{2-6}alkenyl and R^2 is hydrogen or hydroxy.

Preferred compounds include:

2-(2-[2,2,2-trifluoroethoxy]phenyl)purin-6-one,
2-(2-cyclopropylmethoxyphenyl)purin-6-one,
2-(2-cyclopropylmethoxyphenyl)purin-8,8-dione,
2-(2-benzyloxyphenyl)purin-6,8-dione,
2-(2-propoxyphenyl)-8-trifluoromethylpurin-8-one,
2-(2-propoxyphenyl)-8-phenylpurin-6-one,
2-(2-propoxyphenyl)-8-methylpurin-6-one,
2-(2-propoxyphenyl)-8-mercaptopurin-6-one,
2-(2-propoxyphenyl)-8-methylthiopurin-6-one,
2-(2-propoxyphenyl)-8-aminopurin-6-one,
2-(2-propoxy-5-nitrophenyl)purin-6-one,
2-(2-propoxy-5-aminophenyl)purin-6-one,
2-(2-propoxy-5-acetamidophenyl)purin-6-one,
2-(2-propoxy-4-methoxyphenyl)purin-6-one,
2-(2-propoxy-5-methoxyphenyl)purin-6-one,
2-(2-propoxy-5-chlorophenyl)purin-6-one,
2-(2-propoxy-4-methylphenyl)purin-6-one,
2-(2-propoxy-5-fluorophenyl)purin-6-one,
2-(2-propoxy-5-dimethylsulphamoylphenyl)purin-6-one,
2-(2-propoxy-5-methylsulphamoylphenyl)purin-6-one,
2-(2-propoxy-5-sulphamoylphenyl)purin-6-one,
2-(2-propoxy-4-methylthiophenyl)purin-6-one,
2-(2-propoxy-5-cyanophenyl)purin-6-one, or
2-(2-propoxy-5-carbamoylphenyl)purin-6-one,
or a pharmaceutically acceptable salt thereof.

European published application number 0371731, which discloses compounds of the formula



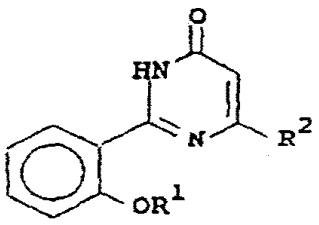
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, phenylC_{1-4}alkyl or C_{1-4}alkyl substituted by 1 to 6 fluoro groups;
R^2 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkoxy, nitro or $-NR^3R^4$; and
R^3 and R^4 are independently hydrogen or C_{1-4}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;
with the proviso that R^1 is not methyl or ethyl when R^2 is hydrogen.

Preferred compounds include:

2-(2-propoxyphenyl)quinazolin-4(3H)-one,
7-methylthio-2-(2-propoxyphenyl)quinazolin-4(3H)-one,
7-nitro-2-(2-propoxyphenyl)-4(3H)-quinazolinone,
7-amino-2-(2-propoxyphenyl)-4(3H)-quinazolinone, or
7-methylamino-2-(2-propoxyphenyl)-4(3H)-quinazolinone
or a pharmaceutically acceptable salt thereof.

European published application number 0395328, which discloses compounds of the formula



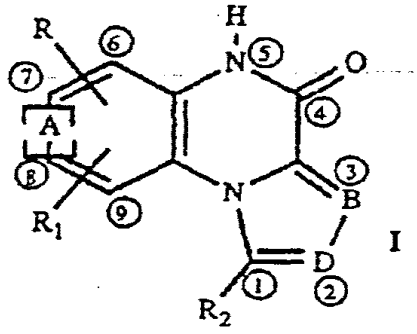
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and
R^2 is C_{1-6}alkyl, phenyl, hydroxy, C_{1-6}alkoxy, halo, -NHCOR^3, -NHCONHR^4, 5-tetrazolyl, -CO_2R^5, cyano, -CONR^{6}R^7, or -NR^{8}R^9 wherein R^3 to R^7 are independently hydrogen or C_{1-6}alkyl and R^8 and R^9 are independently hydrogen or C_{1-6}alkyl optionally substituted by hydroxy provided that the carbon atom adjacent to the nitrogen atom is not substituted by hydroxy;

Preferred compounds include:

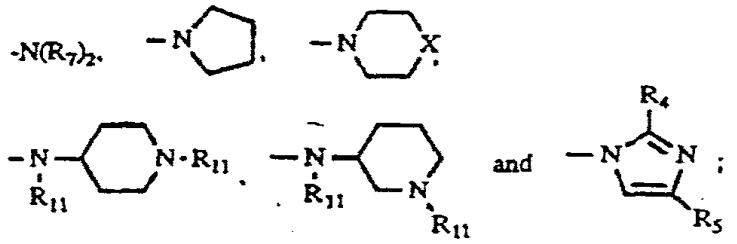
6-amino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-acetamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propionamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-butyramido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-N'-methylureido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4,6-dihydroxy-2-(2-propoxyphenyl)pyrimidine,
4-chloro-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
6-ethylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propylamino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(2-hydroxyethylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-(3-hydroxypropylamino)-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4-hydroxy-6-methyl-2-(2-propoxyphenyl)pyrimidine,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylic acid,
ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxylate,
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
4-cyano-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
2-(2-propoxyphenyl)-6-(1H-tetrazol-5-yl)pyrimidin-4(3H)-one,
4-ethyl-6-hydroxy-2-(2-propoxyphenyl)pyrimidine,
4-hydroxy-6-phenyl-2-(2-propoxyphenyl)pyrimidine,
N-methyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-ethyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
N-propyl 6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide,
6-ethoxy-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
6-N,N-bis-(2-hydroxyethyl)amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

European published application number 0400583, which discloses compounds of the formula

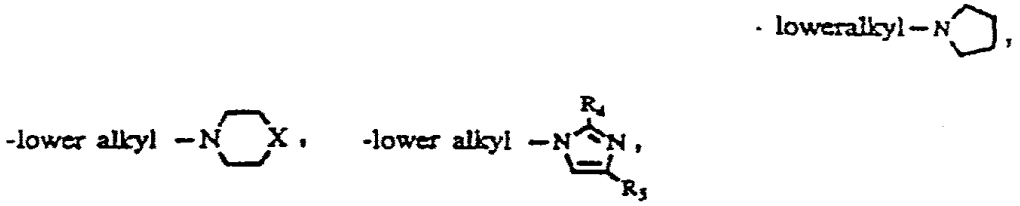


I

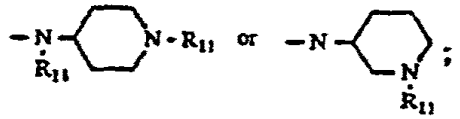
wherein -
A is N or CH;
B is N CR_3;
D is N or CR_2;
R, R_1, are the same or independently hydrogen, hydroxy, loweralkyl, lower alkoxy, phenyloxy, $R_6S(O)_n$-, W-ALK-Q-,



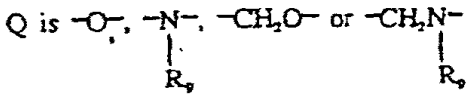
R_2 is hydrogen, lower alkyl, phenyl which may be substituted by up to three methoxy groups, lower alkyl substituted by phenyl which may be substituted by up to three methoxy groups, - lower alkyl $-N(R_8)_2$,

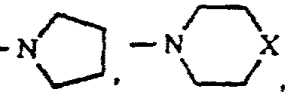


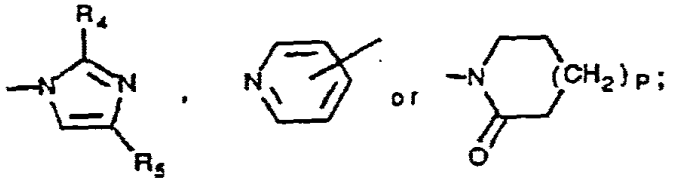
pyridinyl or lower-alkyl pyridinyl;
R_3 is hydrogen, lower alkyl, phenyl, lower alkylphenyl, pyridinyl or loweralkyl pyridinyl;
R_4, R_5 are the same or independently hydrogen or lower alkyl;
R_6 is lower alkyl, phenyl, lower alkylphenyl or pyridinyl;
R_7 are the same or independently hydrogen, loweralkyl, phenyl, pyridinyl,



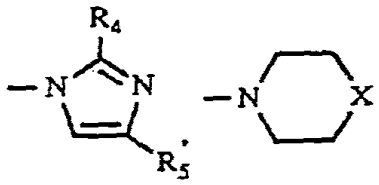
R_8 are the same or independently lower alkyl, phenyl or pyridinyl;

Q is 

W is hydroxy, loweralkoxy, phenoxy, $-N(R_{10})_2$, 



ALK is a C_1-C_4 straight or branched chain alkyl;
R_9 is hydrogen, lower alkyl or phenyl;
R_{10} are the same or independently hydrogen, loweralkyl or phenyl;
R_{11} are the same or independently hydrogen or lower alkyl;
X is $-CH_2-$, $-O-$, $S(O)_n$, $-NR_{10}$;
n is the integer 0, 1 or 2 and
p is the integer 0 or 1.
with the provisos that:
a) one and only one of B or D must be N;
b) when A is CH, when D is N, when B is CR_3 where R_3 is H, when R_2 is hydrogen, lower alkyl or phenyl then R and/or R_1 must be



or W-ALK-Q-;
and the pharmaceutically acceptable salts thereof.

Preferred compounds include:

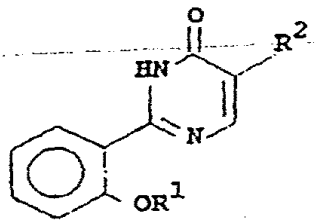
1-ethyl-8-(1H-imidazol-1-yl)-3-methylimidazo[1,5-a]quinoxalin-4-(5H)-one,1-ethyl-8-(1H-imidazol-1-yl)imidazo[1,5-a]quinoxalin-4(5H)-one, 1-ethyl-3-methyl-8-(4-morpholino)-imidazo [1,5-a]quinoxalin-4(5H)-one, 1-ethyl-8-(2-ethyl-4-methyl-1H-imidazol-1-yl)-3-methylimidazo[1,5-a]-quinoxalin-4(5H)-one 1-methyl-8-(2-methyl-1H-imidazol-1-yl)imidazo[1,5a]quinoxalin-4(5H)-one, 8-(1H-imidazol-1-yl)-1-methyl-imidazo[1,5-a]quinoxalin-4(5H)-one, 1-ethyl-3-methyl-8-(pyrrolidin-1-yl)imidazo[1,5-a]quinoxalin-4(5H)-one, 1-((morpholin-4-yl)methyl)imidazo[1,5-a]quinoxalin-4(5H)-one, or 6-ethoxy-1-ethyl-8-(2-ethyl-4-methyl-1H-imidazol-1-yl)-3-methylimidazo[1,5-a]quinoxalin-4(5H)-one,

8-(1H-imidazol-1-yl)imidazo[1,2a]quinoxalin-4(5H)-one imidazo[1,2-a]-quinoxalin-5-(4H)-one, or 2-methylimidazo[1,2-a]quinoxalin-4(5H)-one,

9-ethylimidazo[1,5-a] pyrido[3,2e]pyrazin-6(5H)-one, 9-methyl-2(2-methyl-1H-imidazol-1-yl) imidazo[1,5-a]pyrido [3,2-e]pyrazin-5(6H)-one, 9[(2-ethyl-1H- imidazol-1-yl)methyl]-imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one, or 1-ethylimidazo[1,5-a]pyrido[4,3-e]-pyrazin-4-(5H)-one,

imidazo[1,2-a]pyrido[3,2-e]pyrazin-6(5H)-one, 2-phenylimidazo[1,2-a]-pyrido[2,3-e]pyrazin-4(5H)-one, or 2-(1H-imidazol-1-yl)imidazo[1,2-a]pyrido[3,2-e]pyrazin-6(5H)-one.

European published application number 0400799, which discloses compounds of the formula



(1)

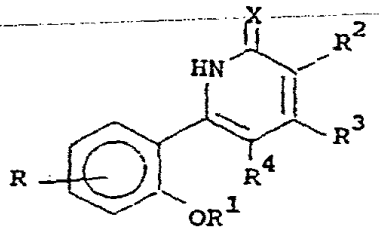
or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-5}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and
R^2 is hydrogen, amino, -NHCOR^3, or -CONR^{4}R^5, wherein R^3 is C_{1-6}alkyl, R^4 is C_{1-6}alkyl and R^5 is hydrogen or C_{1-6}alkyl.

Preferred compounds include:

1,6-dihydro-6-oxo-2-(2-propoxyphenyl)pyrimidine-5-carboxamide,

N-methyl 1,6-dihydro-6-oxo-2-(2-propoxyphenyl)pyrimidine-5-carboxamide,
N,N-dimethyl 1,6-dihydro-6-oxo-2-(2-propoxyphenyl)pyrimidine-5-carboxamide,
5-amino-2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
5-acetamido-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

European published application number 0428268, which discloses compounds of the formula



(1)

or a pharmaceutically acceptable salt thereof, wherein
X is O or S;
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, or C_{1-4}alkyl substituted by 1 to 3 fluoro groups;

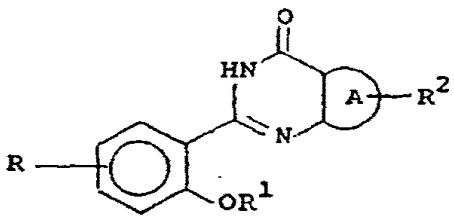
R^2 is hydrogen, -CN, $-CONR^5R^6$, $-CO_2R^7$,5-tetrazolyl, $-NO_2$, $-NH_2$ or $-NHCOR^8$ wherein R^5 to R^8 are independently hydrogen or C_{1-4}alkyl;
R^3 is hydrogen or C_{1-4}alkyl;
R^4 is hydrogen or C_{1-4}alkyl; and
R is halo, C_{1-4}alkyl, C_{1-4}alkoxy, cyano, $-CONR^9R^{10}$, $-CO_2R^{11}$, $-S(O)_nC_{1-4}$alkyl, $-NO_2$, $-NH_2$, $-NHCOR^{12}$, or $-SO_2NR^{13}R^{14}$ wherein n is 0, 1 or 2 and R^9 to R^{14} are independently hydrogen or C_{1-4}alkyl;
with the proviso that R^1 is not methyl when R^2 is $-CO_2H$, $-CO_2CH_2CH_3$ or -CN, X is O, R^3 is hydrogen, R^4 is hydrogen or methyl and R is 6-methoxy.

Preferred compounds include:

3-cyano-6-(2-methoxy-4-methylthiophenyl)-2(1H)-pyridinone,
3-cyano-6-(4-methylthio-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(4-methylthio-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
3-cyano-6-(2-methoxy-4-methylsulphinylphenyl)-2(1H)-pyridinone,
3-cyano-6-(4-methylsulphinyl-2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-6-(4-methylsulphonyl-2-propoxyphenyl)-2(1H)-pyridinone,
3-cyano-6-(2-methoxy-4-methylsulphonylphenyl)-2(1H)-pyridinone,
3-cyano-6-(5-fluoro-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(5-fluoro-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
3-cyano-6-(4-methoxy-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(4-methoxy-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
3-cyano-6-(5-methoxy-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(5-methoxy-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
3-cyano-6-(5-cyano-2-propoxyphenyl)-2(1H)-pyridinone,
3-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
methyl 3-(3-cyano-1,2-dihydro-(2-oxo-6-pyridinyl)-4-propoxybenzoate,
3-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
N-methyl-3-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
N-methyl 3-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
N,N-dimethyl-3-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
N,N-dimethyl 3-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxybenzamide,
4-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-3-propoxybenzonitrile,
4-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-3-propoxybenzamide,

3-cyano-6-(5-methylthio-2-propoxyphenyl)-2(1H)pyridinone,
3-(3-cyano-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxy-N,N-dimethylbenzenesulphonamide,
3-(3-carboxamido-1,2-dihydro-2-oxo-6-pyridinyl)-4-propoxy-N,N-dimethylbenzenesulphonamide,
6-(2-cyclopropylmethoxy-5-flourophenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
6-(5-fluoro-2-(2-methylpropoxy)phenyl)-1,2-dihydro-2-oxopyridine-3-carboxamide,
3-cyano-6-(5-nitro-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(5-nitro-2-propoxyphenyl)-2-oxo-3-pyridinone carboxamide,
3-cyano-6-(5-amino-2-propoxyphenyl)-2(1H)-pyridinone,
1,2-dihydro-6-(5-amino-2-propoxyphenyl)-2-oxo-3-pyridinone carboxamide,
3-cyano-6-(5-acetamido-2-propoxyphenyl)-2(1H)-pyridinone or
1,2-dihydro-6-(5-acetamido-2-propoxyphenyl)-2-oxo-3-pyridine carboxamide,
or a pharmaceutically acceptable salt thereof.

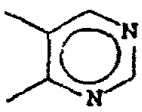
European published application number 0442204, which discloses compounds of the formula



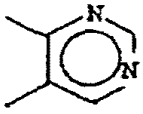
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkyl C_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups ;
R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, -$NHCOR^3$ wherein R^3 is hydrogen or C_{1-6} alkyl, or -NR^4R^5, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-6}cycloalkyl or C_{1-6}alkyl which is optionally substituted by -CF_3, phenyl, -$S(O)_nC_{1-6}$ alkyl wherein
n is 0, 1 or 2, -OR^6, -CO_2R^7 or -NR^8R^9 wherein R^8 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -$S(O)_nC_{1-6}$alkyl, -OR^6 or -NR^8R^9 groups ;
R is halo, C_{1-4}alkyl, C_{1-4}alkoxy, cyano, -$CONR^{10}R^{11}$, CO_2R^{12}, C_{1-4} alkyl$S(O)_n$, -NO_2, -NH_2, -$NHCOR^{13}$ or $SO_2NR^{14}R^{15}$ wherein n is 0, 1 or 2 and R^{10} to R^{15} are independently hydrogen or C_{1-4} alkyl ; and


is a ring of sub-formula (a) or (b) :

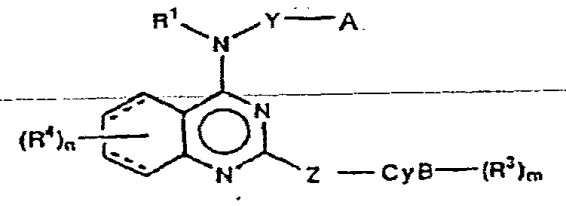


(a)



(b).

European published application number 0579496, which discloses compounds of the formula



(I)

wherein — represents a single or double bond;
R^1 is hydrogen or C_{1-4} alkyl;
Y is a single bond or C_{1-6} alkylene;
A is
(i) -CyA-$(R^2)_t$,
(ii) -O-R^9 or -$S(O)_p$-R^9, or
(iii) -$NR^{16}R^{17}$;
in which R^9 is hydrogen, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl or -CyA-$(R^2)_t$;
R^{16} and R^{17} independently are hydrogen or C_{1-4} alkyl;
p is 0-2;
CyA is
(1) a 3-7 membered, saturated or unsaturated carbocycle,
(2) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,
(3) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and one oxygen atom,
(4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom and two oxygen atoms,
(5) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms and one oxygen atom,
(6) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,
(7) a 4-7 membered, unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms;
R^2 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) -$COOR^5$, in which R^5 is hydrogen or C_{1-4} alkyl, (5) -NR^6R^7, in which R^6 and R^7 independently are hydrogen or C_{1-4} alkyl, (6) -$SO_2NR^6R^7$, in which R^6 and R^7 are as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro or (10) trifluoromethoxy;
Z is a single bond, methylene, ethylene, vinylene or ethynylene;
CyB is
(1) a 4-7 membered, unsaturated or partially saturated heterocycle containing one nitrogen atom,
(2) a 4-7 membered, unsaturated or partially saturated heterocycle containing two nitrogen atoms,
(3) a 4-7 membered, unsaturated or partially saturated heterocycle containing three nitrogen atoms,
(4) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two oxygen atoms,
(5) a 4-7 membered, unsaturated or partially saturated heterocycle containing one or two sulfur atoms,
R^3 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl;
R^4 is (1) hydrogen, (2) C_{1-4} alkyl, (3) C_{1-4} alkoxy, (4) -$COOR^8$, in which R^8 is hydrogen or C_{1-4} alkyl, (5) -NR^9R^{10}, in which R^9 is hydrogen, C_{1-4} alkyl or phenyl(C_{1-4} alkyl) and R^{10} is hydrogen or C_{1-4} alkyl, (6) -$NHCOR^{11}$, in which R^{11} is C_{1-4} alkyl, (7) -$NHSO_2R^{11}$, in which R^{11} is as hereinbefore defined, (8) $SO_2NR^9R^{10}$ in which R^9 and R^{10} are as hereinbefore defined, (9) -$OCOR^{11}$, in which R^{11} is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro, (14) cyano, (15) -$SO_2N{=}CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C_{1-4} alkyl and R^{13} is C_{1-4} alkyl, (16) -$CONR^{14}R^{15}$ in which R^{14} is hydrogen or C_{1-4} alkyl or phenyl(C_{1-4} alkyl) and R^{15} is C_{1-4} alkyl or (17) C_{1-4} alkylthio, (18) C_{1-4} alkylsulfinyl, (19) C_{1-4} alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C_{1-4} alkyl)silylethynyl or (23) acetyl;
and l, m and n independently are 1 or 2;
with the proviso that
(1) CyA-$(R^2)_t$ does not represent cyclopentyl or trifluoromethylphenyl when Y is a single bond,
(2) CyB does not bond to Z through a nitrogen atom when Z is vinylene or ethynylene,
(3) CyB is not pyridine or thiophene when CyA is a 4-7 membered unsaturated, partially saturated or fully saturated heterocycle containing one or two oxygen atoms, and
(4) Y is not a single bond when A is (ii) -O-R^9 or -$S(O)_p$-R^9 or (iii) -$NR^{16}R^{17}$;
or a pharmaceutically acceptable salt thereof, or a hydrate thereof.

Preferred compounds include:

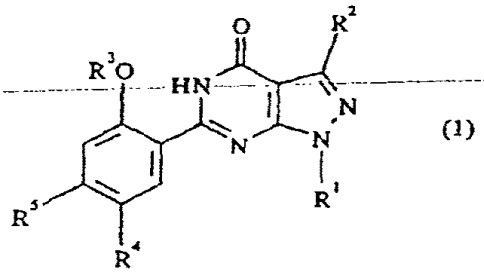
4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-methoxycarbonylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-chlorophenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-nitrophenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-methyl-3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-methoxy-3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-chloro-3-pyridyl)quinazoline,
4-phenylmethylamino-2-(6-trifluoromethyl-3-pyridyl)quinazoline,
4-phenylmethylamino-6-methyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6,7-dimethoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-carboxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxycarbonyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-amino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-(N,N-dimethylamino)-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-acetylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methanesulfonylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-sulfamoyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-acetoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-bromo-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-7-fluoro-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethyl-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethoxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-hydroxy-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-nitro-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-cyano-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-6-methyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6,7-dimethoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-carboxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-methoxycarbonyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-amino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-(N,N-dimethylamino)-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-acetylamino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-methanesulfonylamino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-sulfamoyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-acetoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-chloro-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-bromo-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-7-fluoro-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethyl-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-trifluoromethoxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-hydroxy-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-nitro-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-6-cyano-2-(4-pyridyl)quinazoline,
4-phenylamino-2-(3-pyridyl)quinazoline,
4-(3-methoxycarbonylphenyl)amino-2-(3-pyridyl)quinazoline,
4-phenylethylamino-2-(3-pyridyl)quinazoline,

4-phenylmethylamino-2-(2-pyridyl)quinazoline,
4-phenylmethylamino-2-(4-pyridyl)quinazoline,
4-phenylmethylamino-2-(2-(3-pyridyl)ethyl)quinazoline,
4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline,
6-iodo-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(3-carboxyphenyl)amino-2-(4-pyridyl)quinazoline,
6-fluoro-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(cyclopropylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(cyclohexylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(2-azepinylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-pyridylmethyl)amino-2-(3-pyridyl)quinazoline,
4-((1-methyl-2-pyrrolyl)methyl)amino-2-(3-pyridyl)quinazoline,
4-(3-isoxazolyl)amino-2-(3-pyridyl)quinazoline,
4-(3-isoxazolylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(2-thienylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(2-furylmethyl)amino-2-(1 -imidazolyl)quinazoline,
4-(2-tetrahydrofuranylmethyl)amino-2-(1 -imidazolyl)quinazoline,
4-(4-tetrahdyropyranylmethyl)amino-2-(1 -imidazolyl)quinazoline,
6-methoxy-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(4-tetrahydropyranylmethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-thienylmethyl)amino-2-(1 -imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
4-(1,1-dimethyl-2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-methoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
4-(3-ethoxypropyl)amino-2-(1-imidazolyl)quinazoline,
6-nitro-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-ethoxyethyl)amino-2-(3-pyridyl)quinazoline,
6,7-dimethoxy-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-dimethylaminoethyl)amino-2-(1-imidazolyl)quinazoline,
6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methoxy-2-(2-methyl-1-imidazolyl)quinazoline,
4-(2-hydroxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6,8-diiodo-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methylsulfonyl-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)-quinazoline,
2-(1-imidazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline,
6-acetyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,
6-ethynyl-4-(2-methoxyethyl)amino-2-(3-pyridyl)quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)quinazoline,
4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-methoxycarbony1-2-(-imidazolyl)-quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)-quinazoline,
4-(2-methoxyethyl)amino-6-hydroxymethyl-2-(1-imidazolyl)quinazoline,
4-(2-methoxyethyl)amino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline,
4-(3-methoxypropyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropyl- silylethynyl)-quinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylquinazoline,
4-phenylmethylamino-6-methyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6,7-dimethoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-carboxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline,

4-phenylmethylamino-6-amino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-(N,N-dimethylamino)-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-acetylamino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-methanesulfonylamino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-sulfamoyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-acetoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-bromo-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-7-fluoro-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-trifluoromethyl-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-trifluoromethoxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-hydroxy-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-nitro-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-6-cyano-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline,
4-phenylmethylamino-2-(2-methyl-1 -imidazolyl)quinazoline,
6-bromo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
7-chloro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-chloro-4-phenylamino-2-(1-imidazolylmethyl)quinazoline,
6-nitro-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-methoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline,
6-chloro-4-(3-carboxyphenyl)amino-2-(1 -imidazolylmethyl)quinazoline,
6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6,7-dimethoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
6-dimethylaminomethylideneaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-(phenylmethylaminosulfonyl)-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(2-phenylethyl)amino-2-(1 -imidazolyl)quinazoline,
4-cyclohexylmethylamino-2-(1 -imidazolyl)quinazoline,
6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-phenylmethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-iodo-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(4-trifuloromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
4-phenylmethylamino-2-(2-azepinyl)quinazoline,
4-phenylmethylamino-2-(1,5-diazepin-2-yl)quinazoline,
4-phenylmethylamino-2-(2-pyrimidinyl)quinazoline,
4-phenylmethylamino-2-(2-triazinyl)quinazoline,

4-phenylmethylamino-2-(2-pyrrolyl)quinazoline,
4-phenylmethylamino-2-(1-triazolyl)quinazoline,
6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(3-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline
4-phenylmethylamino-6,8-diiodo-2-(1-imidazolyl)quinazoline,
4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
6-hydroxymethyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline
6-methylthio-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
6-methylsulfinyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
6-methylsulfinyl-4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-phenylmethylamino-2-(2-thienyl)quinazoline,
4-phenylmethylamino-2-(2-furyl)quinazoline,
4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-carboxy-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-ethoxycarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
4-(2-methoxyethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline or
4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline.

European published application number 0636626, which discloses compounds of the formula



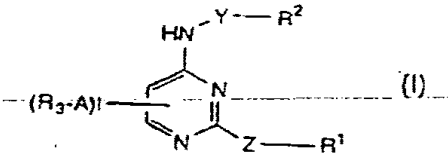
(1)

and salts and solvates (e.g. hydrates) thereof, in which:
R^1 represents arylmethyl or C_{1-6}alkyl optionally substituted by one or more fluorine atoms;
R^2 represents methyl;
R^3 represents C_{2-4}alkyl;
R^4 represents nitro, cyano, C_{1-6}alkoxy, $C(=X)NR^6R^7$, NR^8R^9, $(CH_2)_mNR^{10}C(=Y)R^{11}$ or a 5-membered heterocyclic ring selected from thienyl, thiazolyl and 1,2,4-triazolyl each ring optionally substituted by a C_{1-4}alkyl or aryl group; or when R^1 is arylmethyl or C_{1-6}alkyl substituted by one or more fluorine atoms then R^4 may also represent hydrogen;
R^5 represents hydrogen or C_{1-6}alkyl;
R^6 represents hydrogen or C_{1-6}alkyl;
R^7 represents hydrogen, amino, hydroxyl, C_{1-6}alkyl, aryl or arylC_{1-4}alkyl;
R^8 represents hydrogen or C_{1-6}alkyl;
R^9 represents hydrogen, C_{1-6}alkyl, SO_2R^{12}, CO_2R^{12}, $C(=NCN)SR^{12}$ or $C(=NCN)NR^{13}R^{14}$;
R^{10} represents hydrogen or C_{1-6}alkyl;
R^{11} represents C_{1-6}alkyl optionally substituted by one or more halogen atoms, or R^{11} represents aryl, arylC_{1-4}alkyl, thienyl, $NR^{15}R^{16}$, $CH_2NR^{17}R^{18}$ or R^{10} and R^{11} together represent $-A(CH_2)_n-$;
R^{12} represents C_{1-6}alkyl, aryl or arylC_{1-4}alkyl;
R^{13} represents hydrogen or C_{1-6}alkyl;
R^{14} represents hydrogen, C_{1-6}alkyl, aryl, arylC_{1-4}alkyl or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a morpholine, piperazine or N-C_{1-4}alkylpiperazine ring;
R^{15} represents hydrogen or C_{1-6}alkyl or R^{10} and R^{15} together represent $-A(CH_2)_n-$;
R^{16} represents hydrogen, C_{1-6}alkyl, aryl, arylC_{1-4}alkyl, CO_2R^{12}, $CH_2CO_2R^{12}$ or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a morpholine, piperazine or N-C_{1-4}alkylpiperazine ring;
R^{17} represents hydrogen or C_{1-6}alkyl;
R^{18} represents hydrogen, C_{1-6}alkyl, aryl, arylC_{1-4}alkyl, COR^{12} or R^{17} and R^{18} together with the nitrogen atom to which they are attached form a morpholine, piperazine or N-C_{1-4}alkylpiperazine ring;
A represents CH_2 or C=O;
m represents zero or 1;
n represents 1,2 or 3;
X represents S or NH, or when R^7 represents amino then X may also represent O;
Y represents O or S; for use in therapy.

Preferred compounds include:

1,3-Dimethyl-6-(2-propoxy-5-acetamidophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1-ethyl-3-methyl-6-[2-propoxy-5-(4-methyl-2-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1-ethyl-3-methyl-6-[2-propoxy-5-(2-methyl-4-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1-ethyl-3-methyl-6-[2-propoxy-5-(2-(3-pyridyl)-4-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1,3-dimethyl-6-[2-propoxy-5-(2-methyl-4-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1,3-dimethyl-6-[2-propoxy-5-(3-phenyl-1,2,4-triazol-5-yl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1,3-dimethyl-6-(2-propoxy-5-methanesulfonamidophenyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one;
and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

European published application number 0640599, which discloses compounds of the formula



wherein A is a bond, C1-4 alkylene or C1-4 oxyalkylene;
Y is a bond, C1-4 alkylene, C1-4 alkyleneoxy, C1-4 alkoxyphenylene or phenyl(C1-4)alkylene;
Z is a bond or vinylene;

R1 is 4-15 membered heterocyclic ring containing one or two nitrogen atoms optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl and nitro;

R2 is (i) 4-15 membered heterocyclic ring containing one or two hetero atoms chosen from nitrogen, oxygen, and sulphur, not more than one hetero atom being sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro and groups of formula:

-COOR10

wherein R10 is hydrogen or C1-4 alkyl,
(ii) C4-15 carbocyclic ring,
(iii) C1-4 alkoxy,
(iv) hydroxy(C1-4 alkoxy) or
(v) hydroxy;

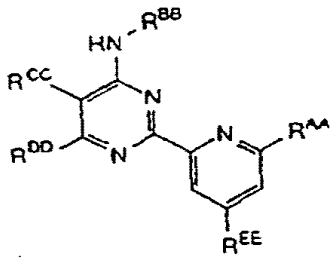
R3 is (i) 4-15 membered heterocyclic ring containing one or two hetero atoms chosen from nitrogen, oxygen and sulphur, not more than one hetero atom being oxgen or sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro, cyano, ethynyl and groups of formula:

-SONR7R8

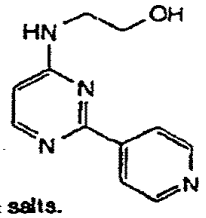
wherein R7 and R8 are independently hydrogen or C1-4 alkyl.
(ii) C4-15 carbocyclic ring,
(iii) a group of formula:

CH2=CH(X)-

wherein X is halogen, or
(iv) hydrogen,
and l is 1 or 2,
provided that: R2 is not hydroxy when Y is a bond; R1 is not bonded through its nitrogen atom when Z is vinylene; and excluding compounds of the formula:



wherein R^{AA} is methyl or n-propyl;
R^{BB} is cyclopentyl, cyclohexyl, 2-hydroxyethyl, methoxyethyl, 2-(1-piperidinyl)ethyl, or phenyl or benzyl which may be substituted by 1 or 2 of methyl, methoxy, chloro, nitro and trifluoromethyl;
R^{CC} is hydrogen or methyl;
R^{DD} is methyl or n-propyl, isopropyl or benzyl; and
R^{EE} is hydrogen or methyl;
and the compound of formula:



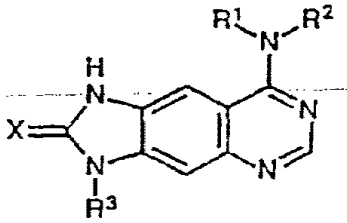
and its pharmaceutically acceptable salts.

Preferred compounds include:

2-(1-Imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-5-(3-methoxyphenyl)-methylpyrimidine,
2-(1-Imidazolyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-4-(2-methoxyethyl)aminopyrimidine,
2-(1-Imidazolyl)-5-ethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-phenylmethyl-4-phenylmethylaminopyrimidine
2-(1-Imidazolyl)-5-methyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5,6-dimethyl-4-phenylmethylaminopyrimidine

2-(1-Imidazolyl)-5-(3-methoxyphenyl)methyl-4-(2-methoxyethyl)amino-pyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-[2-(2-hydroxyethoxy)ethyl]-aminopyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-(2-methoxyethyl)amino-pyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-phenylmethylamino-pyrimidine,
2-(1-Imidazolyl)-5-phenoxymethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(1-imidazolyl)methyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(1-chlorovinyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thiazolyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-[2-(2-hydroxyethoxy)ethyl] aminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1-naphthyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-methoxyphenyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-methoxyphenyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-furyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-thienyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-pyridyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-methoxyethyl) aminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-phenylmethoxyaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-chlorophenyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-chlorophenyl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-methylphenyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(5-methyl-2-thienyl)-4-(1,3-dioxaindan-5 -yl)methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-[4-(1-imidazolyl)phenyl] methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(3-pyridyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-furyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-pyridyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-chlorophenyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(Benzimidazol-1-yl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-ethoxycarbonylphenyl) methylamino-pyrimidine,
2-(1-Imidazolyl)-5-(2-naphthyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(3-Pyridyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylaminopyrimidine,
2-[2-(3-Pyridyl)vinyl]-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl) methylamino-pyrimidine,
2-(2-Methyl-1-imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylamino-pyrimidine or
2-(1-Imidazolyl)-5-(2-thienyl)-4-(benzimidazol-5-yl) methylaminopyrimidine

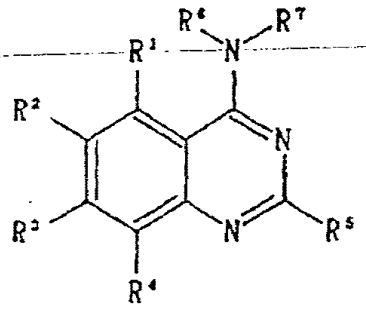
European published application number 0668280, which discloses compounds of the formula



(I)

wherein R^1 and R^2 are the same or different and represent hydrogen, lower alkyl (which is optionally substituted with one to three substituents which are the same or different and are cycloalkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, halogen, alicyclic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aralkyl, aryl optionally substituted with one to three substituents which are the same or different and are lower alkoxy, or aromatic heterocycle group)), cycloalkyl, bicycloalkyl, benzocycloalkyl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), lower alkenyl, aryl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), aromatic heterocycle group-substituted alkyl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl and where said alkyl part is optionally substituted with aryl), aromatic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), or aralkyl (where the aryl part of said aralkyl is optionally substituted with one to three substituents which are the same or different and are lower alkyl, lower alkoxy, dialkyl-substituted amino, halogen, or trifluoromethyl), or R^1 and R^2 are taken together to represent heterocycle group containing nitrogen atom (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aryl, or aralkyl), R^3 represents hydrogen, lower alkyl (which is optionally substituted with one to three substituents which are the same or different and are cycloalkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, halogen, or alicyclic heterocycle group (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, aralkyl, aryl optionally substituted with one to three substituents which are the same or different and are lower alkoxy, or aromatic heterocycle group)), cycloalkyl, lower alkenyl, aryl (which is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), aromatic heterocycle group-substituted alkyl (where said aromatic heterocycle group part is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen or trifluoromethyl, and where the alkyl part is optionally substituted with aryl), aromatic heterocycle group (where said aromatic heterocycle group is optionally substituted with one to three substituents which are the same or different and are lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, amino, monoalkyl-substituted amino, dialkyl-substituted amino, nitro, sulfonamide, halogen, or trifluoromethyl), or aralkyl (where the aryl part of said aralkyl is optionally substituted with one to three substituents which are the same or different and are lower alkyl, lower alkoxy, dialkyl-substituted amino, halogen, or trifluoromethyl), and X represents oxygen atom or sulfur atom, or pharmacologically acceptable salts thereof.

European published application number 0669324, which discloses compounds of the formula



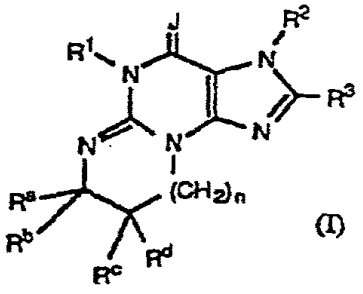
(I)

(wherein R^1, R^2, R^3, R^4 and R^5 may be the same or different from each other and each represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; and

R^6 and R^7 may be the same or different from each other and each represents a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, a lower alkoxyalkyl group, a cyanoalkyl group, a heteroarylalkyl group, a cycloalkyl group, a cycloalkylalkyl group or a carboxyl alkyl group which may be protected, or alternatively R^6 and R^7 may form a ring together with the nitrogen atom to which they are bonded, this ring optionally having a substituent).

or a pharmacologically acceptable salt thereof:

WO91/19717 discloses compounds of the formula



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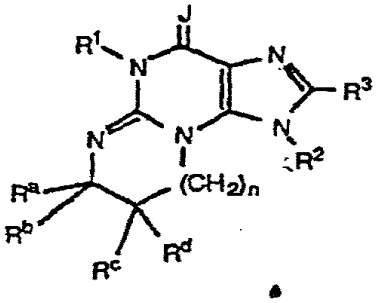
and



(I')

wherein

J is oxygen or sulfur,

R^1 is hydrogen, alkyl or alkyl substituted with aryl or hydroxy;

R^2 is hydrogen, aryl, heteroaryl, cycloalkyl, alkyl or alkyl substituted with aryl, heteroaryl, hydroxy, alkoxy, amino, monoalkyl amino or dialkylamino, or $-(CH_2)_mTCOR^{20}$ wherein m is an integer from 1 to 6, T is oxygen or -NH- and R^{20} is hydrogen, aryl, heteroaryl, alkyl or alkyl substituted with aryl or heteroaryl;

R^3 is hydrogen, halo, trifluoromethyl, alkoxy, alkylthio, alkyl, cycloalkyl, aryl, aminosulfonyl, amino, monoalkylamino, dialkylamino, hydroxyalkylamino, aminoalkylamino, carboxy, alkoxycarbonyl or aminocarbonyl or alkyl substituted with aryl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino;

R^a, R^b, R^c and R^d independently represent hydrogen, alkyl, cycloalkyl or aryl; or (R^a and R^b) or (R^c and R^d) or (R^b and R^c) can complete a saturated ring of 5- to 7- carbon atoms, or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7-carbon atoms, wherein each ring optionally can contain a sulfur or oxygen atom and whose carbon atoms may be optionally substituted with one or more or the following: alkenyl, alkynyl, hydroxy, carboxy, alkoxycarbonyl, alkyl or alkyl substituted with hydroxy, carboxy or alkoxycarbonyl; or such saturated ring can have two adjacent carbon atoms which are shared with an adjoining aryl ring; and

n is zero or one.

Preferred compounds include:

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)-cyclopenta[4,5]imidazo[2,1-b]purin-4-one;

7,8-Dihydro-5-methyl-3-(phenylmethyl)-3*H*-imidazo[2,1-*b*]purin-4(5*H*)-one;

cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-b] purin-4(5*H*)-one;

5,7,8,9-Tetrahydro-5-methyl-3-(phenylmethyl)pyrimido[2,1-b]purin-4(3*H*)-one;

7,8-Dihydro-8-phenyl-5-methyl-3-(phenylmethyl)-3*H*-imidazo[2,1-b]purin-4(5*H*)-one;

5',7'-Dihydro-5'-methyl-3'-(phenylmethyl)spiro[cyclohexane-1,8'-(8*H*)-imidazo[2,1-b]purin]-4'(3'*H*)-one;

cis-5,6a,11,11a-Tetrahydro-5-methyl-3-(phenylmethyl)indeno[1',2':4,5]imidazo[2,1-b]purin-4(3*H*)-one;

5',7'-Dihydro-2',5' dimethyl-3'-(phenylmethyl)spiro{cyclohexane-1,7'(8'H)-imidazo[2,1-b]purin}-4'(3'H)-one;

7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;

cis-5,6a,7,11b-Tetrahydro-5-methyl-3-

(phenylmethyl)indeno[2',1':4,5]imidazo[2,1-b]purin-4(3*H*)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4-(3*H*)-one;
5'-Methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'*H*)-(3'*H*)-imidazo[2,1-b]purin]-4'(5'*H*)-one;
7,8-Dihydro-2,5,7,7-tetramethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5'H)-one;
7,8-Dihydro-7(R)-phenyl-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-3,7(R)-bis(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
(±)-7,8-Dihydro-2,5-dimethyl-7-ethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
6a(S)-7,8,9,10,10a(R)-Hexhydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
6a(R)-7,8,9,10,10a(S)-hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-isopropyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7(R)-trimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
cis-7,7a,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-cyclopenta[5,6]pyrimido[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-(2-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R,S)-(methoxycarbonyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R,S)-(1-propyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
5,7,8,9-Tetrahydro-2,5,7,9(R,S)-pentamethyl-3-(phenylmethyl)-pyrimido[2,1-b]purin-4(3H)-one;
5,6a(*R*),7,8,9,9a(*S*)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
5,6a(*S*),7,8,9,9a(*R*)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-6a,7,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-b]purin-4(5*H*)-one;

5',7'-Dihydro-2',5'-dimethyl-3'-(phenylmethyl)spiro[cyclohexane-1,8'-(8*H*)-imidazo[2,1-b]purin]-4'(3'*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-cyclohept[6,7]imidazo[2,1-b]purin-4(3*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-b]purin-4-(5*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)-3*H*-benzimidazo[2,1-b]purin-4(5*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methylcyclopenta[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopenta[4,5]imidazo[2,1-b]-purin-4(3*H*)-one;

cis-5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-di-methyl-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

2'-Methyl-3'-spiro[cyclopentane-1,7'(8'H)-(3'H]-imidazo[2,1-b]purin}-4'(5'H)-one;

7,8-Dihydro-2,5-dimethyl-7(R)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;

7,8-Dihydro-2,5,7,7-tetramethyl-3H-imidazo[2,1-b]purin-4(5H)-one;

7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;

6a(R),7,8,9,10,10a(S)-Hexahydro-2,5-dimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one;

5',7'-Dihydro-2',5'-dimethylspiro[cyclohexane-1,7'(8'H)-imidazo[2,1-b]purin}-4'(3'H)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3*H*)-thione;

5,6a(*R*),7,8,9,9a(*S*)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-thione;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(4-chlorophenyl-methyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3*H*)-one;

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(cyclohexylmethyl)-

cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(2-naphthylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
bromophenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R)-7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-methoxyphenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,3,5-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(hydroxymethyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-5,6a,7,8,9,9a-Hexahydro-2-methylthio-5-methyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid;
cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid, methyl ester;
cis-5,6a,7,8,9,9a-Hexahydro-2-bromo-5-methyl-3-(phenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(methylaminosulfonyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-1-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methyl-cyclopent[4,5]imidazo[2,1-b]purin-4-(1*H*)one;
cis-5,6a,7,8,9,9a-Hexahydro-3,5-bis-(phenylmethyl) cyclopent(4,5)imidazo(2,1-b)purin-4(3*H*)one;
cis-6a,7,8,9,10,10a-Hexahydro-3,5-bis-(phenylmethyl)-3*H*-benzimidazo[2,1-b]purin-4(5*H*)one;
cis-3-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methyl-cyclopent[4,5]imidazo(2,1-b)purin-4(3*H*)one;
5'-Methyl-3'-(phenylmethyl)spiro[cyclopentane-1,7'(8'*H*)-(3'*H*)-imidazo[2,1-b]purin]-4'(5'*H*)one;
2',5'-Dimethyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'*H*)-(3'H)-imidazo[2,1-b]purin]-4'(5'*H*)one;
cis-5,6a,(R)7,8,9,9a(S)-Hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo(2,1-b)purin-4(3*H*)one;
cis-3-Cyclopentyl-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)one;36
5'-Methyl-2'-trifluoromethyl-3'-(phenylmethyl)spiro[cyclo-pentane-1,7'(8'*H*)-(3'*H*)imidazo[2,1-b]purin]-4'(5'*H*)-one;
7,8-Dihydro-5,7,7-trimethyl-2-trifluoromethyl-3-(phenylmethyl)-3*H*-imidazo[2,1-b]purin-4(5H)-one;

(+/-)-cis-5,6a,7,8,9,9a-Hexahydro-5-m thyl-2-trifluoromethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

(+/-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-(phenylmethyl)-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;

(+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;

(-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5] Imidazo[2,1-b] purin-4(5H)-one;

(+/-) 6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;.

(+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;

(-)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5] imidazo[2,1-b] purin-4(5H)-one;

6a,7,8,9,10,10a,11,12,13,13a-Decahydro-2,5-dimethyl-(3-phenylmethyl)napth[1,8a-d]imidazo[2,1-b]purin-4(5H)one;

7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;

7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;

7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;

7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;

5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[(trimethylacetoxy)methyl]-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-pyridylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[2-(1-morpholinyl)ethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[acetoxymethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

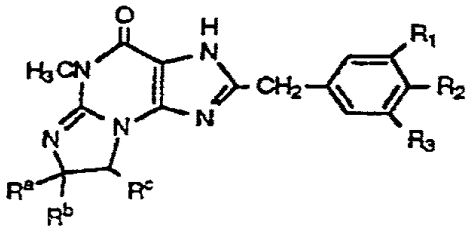
5,6a(*R*),7(*S*),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a(*S*),7(*R*),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one];

cis-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one];

cis-5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one]; or
cis-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one].

WO 94/19351 discloses compounds of the formula



or a pharmaceutically acceptable salt thereof, wherein:

R_1, R_2 and R_3 are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, halogeno, hydroxy, (di-lower alkyl)amino, 4-morpholinyl, 1-pyrrolidinyl, 1-pyrrolyl, $-CF_3$, $-OCF_3$, phenyl and methoxyphenyl; or R_1 and R_2 together are methylenedioxy; or R_1 and R_2 together with the carbon atoms to which they are attached form a benzene ring; and

R^a is hydrogen and R^b and R^c, together with the carbon atoms to which they are attached, form a saturated ring of 5 carbons; or R^a is lower alkyl, R^b is hydrogen or lower alkyl, and R^c is hydrogen; or R^a, R^b and the carbon atom to which they are attached form a saturated ring of 5-7 carbons, and R^c is hydrogen; or R^a is hydrogen, and R^b, R^c and the carbon atoms to which they are attached form a tetrahydrofuran ring; or R^a and R^b, together with the carbon atom to which they are attached, and R^b and R^c, together with the carbon atoms to which they are attached, each form a saturated ring of 5-7 carbons.

Preferred compounds include:

2'-benzyl-spiro[cyclopentane-1',7' (8'H)-[3'H]-imidazo[2,1-b]purin-4'-(5'H)-one;

2'-benzyl-5,7,7-trimethyl-3H-imidazo[2,1-b]purin-4-(5H)-one;

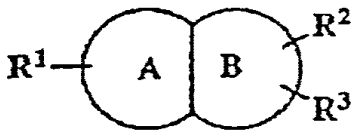
(+)-2-benzyl-7, 8-dihydro-5-methyl-7-(1-methylethyl)-1H-imidazo[2,1-b]-purin-4(5H)-one;

(+,-)-6a, 7, 8, 9, 9a, 10, 11, 11a-octahydro-5-methyl-2-(3,4-methylene-dioxyphenylmethyl)-3H-pentalen[6a,1:4,5]imidazo[2,1-b]purin-4(5H)-one; and

(+)-cis-6a, 7, 9, 9a-tetrahydro-5-methyl-2-[4-(trifluoromethyl)-phenylmethyl]-3H-furo[3', 4':4,5]imidazo[2,1-b]purin-4(5H)-one.

WO 94/22855 discloses compounds of the formula

1. A nitrogen-containing fused-heterocyclic compound having the formula (I) or a pharmacologically acceptable salt thereof:



(I)

in which ring A represents a benzene, pyridine or cyclohexane ring and B represents a pyridine, imidazole or pyrimidine ring, with the proviso that rings A and B are bonded to each other with two atoms being shared by them, and the shared atoms may be any of carbon and nitrogen atoms;

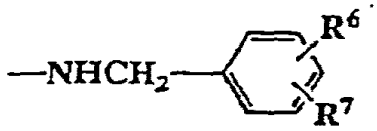
R^1 represents a group represented by the formula: $-NR^4R^5$ (wherein R^4 and R^5 may be the same or different

from each other and each represent a hydrogen atom, a lower alkyl or acyl group or a carboxyl group which may be protected, or alternatively R^4 and R^5 may form a ring together with the nitrogen atom to which they are bonded, provided that the ring may be substituted), or a heteroaryl group which has one or two nitrogen atoms and may be substituted;

R^2 represents a hydrogen atom, a group represented by the formula:

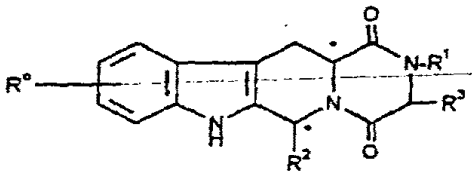
(wherein R^8 represents a carboxyl or tetrazolyl group which may be protected),
or a halogen atom;
and

R^3 represents a hydrogen atom or a group represented by the formula:



(wherein R^6 and R^7 each represent a hydrogen or halogen atom or a lower alkoxy group, or alternatively R^6 and R^7 may together form a methylenedioxy or ethylenedioxy group).

WO 95/19978 discloses compounds of the formula

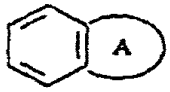


(I)

and salts and solvates thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 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

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

Preferred compounds include:

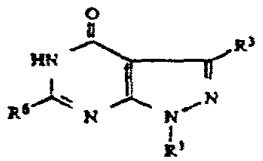
Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2', 1' : 6,1]pyrido[3,4-b]indole-1,4-dione;

Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-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;
(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)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
and physiologically acceptable salts and solvates thereof.

U.S. Patent No. 5,294,612 discloses compounds of the formula



wherein:

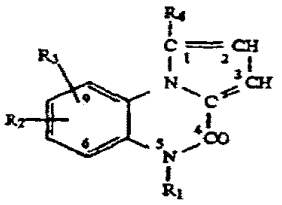
R^1 is hydrogen, alkyl, C_4 to C_7 cycloalkyl, C_4 to C_7 cycloalkyl substituted by C_1 to C_{10} alkyl or hydroxyl, 2- or 3-tetrahydrofuranyl, 3-tetrahydrothienyl 1,1, -dioxide, C_4 to C_7 cycloalkyl-C_1 to C_{10} alkyl, carboxy-C_1 to C_{10} alkyl, carbo-C_1 to C_4 lower-alkoxy-C_1 to C_{10} alkyl, dialkylamino C_1 to C_{10} alkyl, phenyl-C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl in which the phenyl ring is substituted in the 2, 3, or 4-position by one or two substituents, the same or different, selected from the group consisting of amino, halogen, C_1 to C_{10} alkyl, carboxyl, carbo-C_1 to C_4 lower-alkoxy, carbamoyl, $NHSO_2$-(quinolinyl), nitro and cyano:

R^3 is, C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl, lower-alkoxyphenyl-C_1 to C_4 lower-alkyl, diC_1 to C_4 lower-alkoxy-phenyl-C_1 to C_4 lower-alkyl, pyridyl-C_1 to C_4 lower-alkyl, C_4 to C_7 cycloalkyl-C_1 to C_4 lower-alkyl, phenylamino, diC_1 to C_{10} alkylamino, halogen, trifluoromethyl, C_1 to C_4 lower-alkylthio, cyano or nitro; and

R^6 is a nine or ten membered bicyclic ring having carbon and from one to two nitrogen atoms, and

the heterocycle is made up of fused 5 or 6 membered rings or such ring substituted at any available carbon atom by one or two substituents, the same or different, selected from the group consisting of C_1 to C_4 lower-alkyl, halogen, C_1 to C_4 lower-alkoxy, C_4 to C_7 cycloalkyloxy, 4-morpholinyl, C_1 to C_4 lower-alkoxy-C_1 to C_4 lower-alkoxy, hydroxy, imidazolyl, oxo and 4-morpholinyl-C_1 to C_4 lower-alkoxy, or at any available nitrogen atom by C_1 to C_4 lower-alkyl, C_2 to C_4 lower-alkanoyl, or trifluoroacetyl; or a pharmaceutically acceptable acid-addition salt thereof.

U.S. Patent No. 5,405,847 discloses compounds of the formula



I

where the benzo ring can also contain a nitrogen atom instead of a CH group either in position 6, 7, 8 or 9 and the radicals R_1, R_2, R_3 and R_4 have the following meanings:

R_1: C_2–C_6-alkenyl, C_2–C_6-alkynyl, hydroxy, C_1–C_6-alkoxy, C_3–C_6-alkenyloxy, C_3–C_6-alkynyloxy, C_2–C_6-alkanoyloxy, benzoyloxy, morpholinocarbonyloxy, C_1–C_6-alkyloxycarbonyloxy, C_1–C_6-alkylaminocarbonyloxy, C_1–C_6-dialkylaminocarbonyloxy or the group

-Alk-A

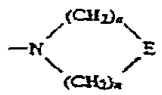
where Alk: is C_1–C_6-alkyl, C_2–C_6-hydroxyalkyl or C_3–C_6-cycloalkyl and the symbol A represents:

1) Hydrogen, halogen, hydroxy, C_1–C_6-alkoxy, C_2–C_6-alkanoyloxy, phenyl;
2) —NHR_5, —NR_5R_6, $NR_5R_6R_7$, pyridylamino, imidazolyl, pyrrolidinyl, N—C_1–C_6-alkylpyrrolidinyl, piperidylamino, N-(phenyl-C_1–C_4-alkyl)-piperidylamino where R_5 and R_6 may be the same or different and represent hydrogen, C_1–C_6-alkyl, C_3–C_7-cycloalkyl, C_3–C_7-hydroxycycloalkyl, morpholino-C_1–C_6-alkyl, phenyl, phenyl-C_1–C_6-alkyl or phenyl-C_2–C_6-oxyalkyl, it also being possible for the phenyl radicals in R_5 and R_6 to be substituted by halogen and R_7 is hydrogen or C_1–C_6-alkyl;
3) The group:

-CO-D

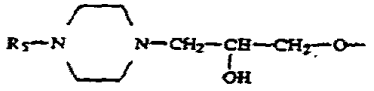
where D is phenyl, C_1–C_6-alkyl, C_3–C_7-cycloalkyl, hydroxy, C_1–C_6-alkoxy, C_3–C_7-cycloalkyloxy, morpholino, pyrrolidino, piperidino, homopiperidino, piperazino, —NHR_5 or —NR_5R_6 and R_5 and R_6 have the meanings given hereinabove;

4) The group:

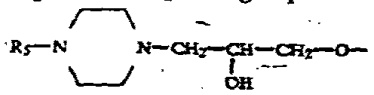


where n can be the integers 1-3 and E represents CH_2, oxygen, sulfur, NH, CHOH, CH—C_1-C_6-alkyloxy, CH—C_2-C_6-alkanoyloxy, CHC_6H_5, CHCOD, CH—$CH_2C_6H_5$, N—C_1-C_6-alkyl, N—C_1-C_6-hydroxyalkyl, N—C_6H_5, N—$CH_2C_6H_5$, N—$CH(C_6H_5)_2$, N—$(CH_2)_2$—OH, N—$(CH_2)_3$—OH or NCOD and the phenyl radicals (C_6H_5) may also be substituted by halogen, C_1-C_6-alkoxy, trifluoromethyl, C_1-C_6-alkyl, methylenedioxy or cyan and D has the meanings given hereinabove;

R_2 and R_3, which may be the same or different: hydrogen, halogen, hydroxy, C_1-C_6-alkyl, trifluoromethyl, —CN, C_1-C_6-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, —NHR_5, —NR_5R_6, $NR_5R_6R_7$ (meanings R_5, R_6, R_7 as given hereinabove) or the group -G-Alk-A, where Alk and A have the meanings given hereinabove and G is oxygen, sulfur, NH or NR_5 and R_2 can also be

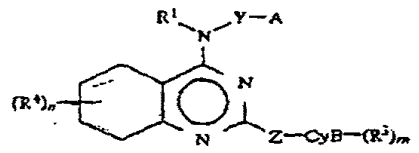


R_4: hydrogen or halogen, where R_1 can also be hydrogen, when R_2 is the group



and R_5 represents phenyl, C_1-C_4-alkoxyphenyl or diphenylmethyl and R_3 and R_4 are hydrogen, and their physiologically acceptable acid addition salts and quaternary ammonium salts, with the exception of the compounds of Formula I where R_1 is methyl, dimethylaminopropyl, dimethylaminoethyl, morpholinoethyl or pyrrolidinoethyl, R_2, R_3 and R_4 are hydrogen and the benzo ring does not contain a nitrogen atom instead of a CH group.

U.S. Patent No. 5,436,233 discloses compounds of the formula



(I)

wherein R^1 is hydrogen or C1–4 alkyl;
Y is single bond or C1-6 alkylene;
A is
(i) —CyA—$(R^2)_l$,
(ii) —O—R^0 or —$S(O)_p$—R^0,
in which R^0 is R^{0A} or R^{0B};
R^{0A} is —CyA—$(R^2)_l$;
R^{0B} is hydrogen or C1–4 alkyl;
p is 0-2;
CyA is
(1) 3–7 membered, saturated or unsaturated, monocyclic carbocyclic ring,

(2) 7-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one nitrogen atom, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,
(3) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,
(4) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as a hetero atom, one nitrogen atom,
(5) 4- or 5-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one nitrogen atom, one nitrogen and one oxygen atoms, two nitrogen and one oxygen atoms, or one nitrogen and two oxygen atoms,
(6) 4–7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one or two sulfur atoms or
(7) 4–7 membered, unsaturated or partially or fully saturated, monocyclic hetero ring containing as hetero atoms, one or two oxygen atom;

R^2 is R^{2A} or R^2B;

R^{2A} is (1) $—NR^6AR^{7A}$, in which R^{6A} and R^{7A} independently are hydrogen or C1–4 alkyl (with the proviso that R^{6A} and R^{7A} are not hydrogen at same time), (2) $—SO_2NR^6R^7$, in which R^6 and R^7 independently are hydrogen or C1–4 alkyl, (3) trifluoromethyl or (4) trifluoromethoxy;

R^{2B} is (1) hydrogen, (2) C1–4 alkyl, (3) C1–4 alkoxy, (4) $—COOR^5$, in which R^5 is hydrogen or C1–4 alkyl, (5) halogen, (6) nitro or (7) $—NRGBR^{7B}$, in which $R^{6B}$and R^{7B} are hydrogen;

Z is Z^A or Z^B;

Z^A is methylene, ethylene, vinylene or ethynylene;

Z^B is single bond;

CyB is
(1) 7-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one, two or three nitrogen atoms,
(2) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, two or three nitrogen atoms,
(3) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as a hetero atom, one nitrogen atom,
(4) 4- or 5-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one, two or three nitrogen atoms, or
(5) 4–7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one or two oxygen atoms, or one or two sulfur atoms;

R^3 is hydrogen, C1–4 alkyl, C1–4 alkoxy, halogen or trifluoromethyl;

R^4 is R^{4A} or R^{4B};

R^{4A} is (1) $—NHSO_2R^{11}$, in which R^{11} is C1–4 alkyl, (2) $SO_2NR^9R^{10}$, in which

R^9 is hydrogen, C1–4 alkyl or phenyl(C1–4 alkyl) and R^{10} is hydrogen or C1–4 alkyl, (3) $—OCOR^{11}$, in which R^{11} is as hereinbefore defined, (4) hydroxy, (5) $—SO_2N=CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C1–4 alkyl and R^{13} is C1–4 alkyl, (6) $—CONR^{14}R^{15}$ in which R^{14} is hydrogen or C1–4 alkyl and R^{15} is C1–4 alkyl or phenyl(C1–4 alkyl), (7) ethynyl, (8) tri(C1–4 alkyl)silylethynyl or (9) acetyl;

R^{4B} is (1) hydrogen, (2) C1–4 alkyl, (3) C1–4 alkoxy, (4) —$COOR^8$, in which R^8 is hydrogen or C1–4 alkyl, (5) —NR^9R^{10}, in which R^9 and R^{10} are as hereinbefore defined, (6) —$NHCOR^{11}$, in which R^{11} is as hereinbefore defined, (7) halogen, (8) trifluoromethyl, (9) nitro, (10) cyano, (11) C1–4 alkylthio, (12) C1–4 alkylsulfinyl, (13) C1–4 alkylsulfonyl, (14) hydroxymethyl, and l, m and n independently are 1 or 2; with the proviso that

(1) the group of the formula: —CyA—$(R^2)_l$ does not represent a cyclopentyl and trifluoromethylphenyl group when Y is a single bond, that

(2) a CyB ring does not bond to Z through a nitrogen atom in the CyB ring when Z is vinylene or ethynylene, that

(3) a CyB ring is not pyridine or thiophene when CyA is a ring of CyA—(7) that

(4) Y is not a single bond, when A is (ii) —O—R^0 or —$S(O)_p$—R^0 and that

(5) A is not —CyA—$(R^2B)l$ and —OR^{0B}, when Z is Z^B and R^4 is R^{4B}; or pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

Preferred compounds include:

4-phenylmethylamino-2-((1-imidazolyl)methyl)-quinazoline,
4-phenylmethylamino-2-((1-imidazolyl)methyl)-quinazoline,
6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline,
6-chloro-4-phenylamino-2-(1-imidazolylmethyl)-quinazoline,
6-chloro-4-(3-carboxyphenyl)amino-2-(1-imidazolylmethyl)quinazoline
or
4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline,

and pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-dimethylaminomethylideneaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-(phenylmethylaminosulfonyl)-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-phenylmethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6-ethylaminocarbonyl-4-phenylmethylamino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline,
6-hydroxy-4-phenylmethylamino-2-(1-imidazolyl)-quinazoline,
6-(1-i midazolyl)-4-(2-methoxyethyl)amino-6-(2-triethylsilylethynyl)quinazoline,
6-ethynyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,
6-(1-imidazolyl)-4-phenylmethylamino-6-ethynyl-quinazoline or
6-acetyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)-quinazoline,

and pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,

4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,

4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,

4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,

4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,

4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)-quinazoline,

4-(4-trifuloromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,

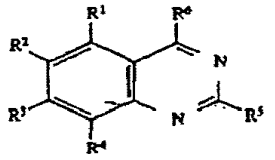
4-(3-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,

4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline or

4-(2-phenoxyethyl)amino-2-(1-imidazolyl)quinazoline,

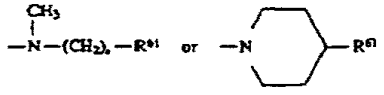
and pharmaceutically acceptable acid addition salts

U.S. Patent No. 5,576,322 discloses compounds of the formula

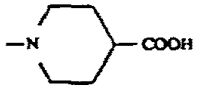


(I)

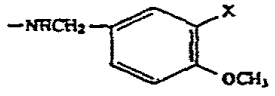
wherein R1, R3, and R4, each of which may be the same or different from each other, may each represent a hydrogen atom, a halogen atom or a lower alkyl group or a lower alkoxy hydrogen atom, R2 is a halogen or cyan group R5 is a group represented by the formula:



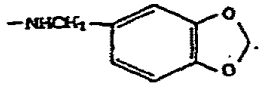
wherein u is 3 or 4 and R61 represents a carboxyl group which may be protected or a heternaryl group; or R5 is a group represented by the formula:



and R6 is a group represented by the formula



wherein X is hydrogen atom or a halogen atom or



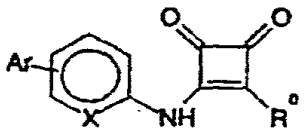
or the pharmacologically acceptable salt thereof

Preferred compounds include:

2-(4-carboxypiperidino)-4-(3,4-methylene-dioxybenzyl) amino-6-chloroquinazoline- or a pharmaceutically acceptable salt thereof.

Sodium 2-(4-carboxypiperidino)-4-(3,4-methylene-dioxybenzyl) amino-6-chloroquinazoline.

WO 94/29277 discloses compounds of the formula



Formula (1)

or a pharmaceutically acceptable salt thereof, wherein

Ar is an optionally substituted aryl or heteroaryl ring selected from phenyl, naphthyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, imidazolyl, thienyl, oxazolyl, benzimidazolyl, benzoxazolyl, indolyl or thianaphthenyl,

X is CH or N;

R^0 is NR^1R^2 or hydrogen; and

R^1 and R^2 are independently hydrogen or C_{1-6}alkyl.

Preferred compounds include:

3-amino-4-[4-(3-pyridyl)]anilino-3-cyclobutene-1,2-dione,

3-amino-4-[3-(4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-methylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-dimethylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(3-methyl-4-pyridyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-oxazolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(4-pyridyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(3-pyridyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-pyridyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-thienyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(3-thienyl)anilin]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-thianaphthenyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(5-pyrimidyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-benzoxazoyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-benzimidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-indolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-(3-phenyl)anilino-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-hydroxyphenyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(2-methoxyphenyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[3-(3-hydroxy-2-pyridyl)anilino]-3-cyclobutene-1,2-dione,

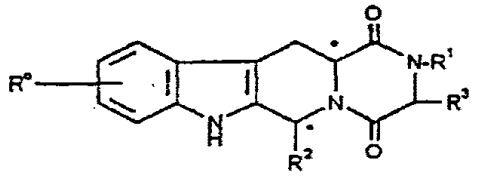
3-amino-4-[3-(2-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

3-amino-4-[6-(4-pyridyl)-2-pyridylamino]-3-cyclobutene-1,2-dione, or

3-[3-(4-pyridyl)anilino]-3-cyclobutene-1,2-dione,

or a pharmaceutically acceptable salt thereof.

WO 95/19978 discloses compounds of the formula



(I)

and salts and solvates thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring 

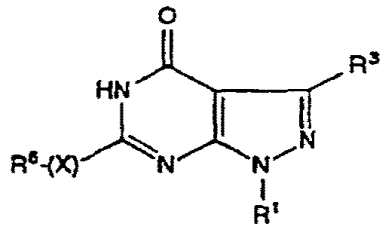
attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

Preferred compounds 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[3,4-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;
(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)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
and physiologically acceptable salts and solvates thereof.

WO 96/28429 discloses compounds of the formula



wherein:

R^1 is tert-butyl, or cyclopentyl;

R^3 is methyl, ethyl, or phenylmethyl;

X is $-CH_2-$, $-O-$, or $-NH-$; and

R^6 is phenyl (or phenyl substituted by from one to three, the same or different, substituents selected from the group

consisting of lower-alkoxy, hydroxy, halogen, carboxylower-alkoxy, 4-morpholinyl-lower-alkoxy, 5-tetrazolyl-lower-alkoxy, dilower-alkylamino, trifluoromethyl, nitro, amino, lower-alkylsulfonylamino, dilower-alkylamino-lower-alkylphenyl carbonyloxy, and 1-imidazolyl); or when X is $-CH_2-$ R^6 is additionally 2-,3-, or 4-pyridinyl, 1-pyrrolyl, 1-benzimidazolyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1,2,3,4-tetrahydro-1-quinolinyl, hydroxy, 1-imidazolyl, 1-lower-alkyl-2,3,4, or 5-pyrrolyl, 1-pyrazolyl, 3-,4-, or 5-isoxazolyl(or 3,4, or 5-isoxazolyl substituted on any available carbon atom thereof by lower-alkyl), 2-thienyl, or 3-thienyl; or a pharmaceutically acceptable acid-addition salt and/or hydrate thereof.

Preferred compounds include:

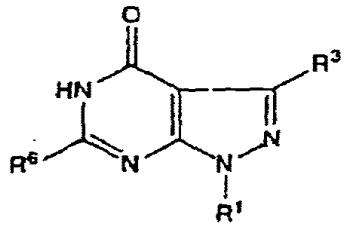
1-cyclopentyl-3-ethyl-6-(4-methoxyphenylmethyl)pyrazolo [3,4-d]pyrimindin-4-one,

1-cyclopentyl-3-ethyl-6-(4-hydroxyphenylmethyl)pyrazolo [3,4-d]pyrimindin-4-one,

1-cyclopentyl-3-ethyl-6-(phenylmethyl)pyrazolo[3,4-d] pyrimindin-4-one, and

1-cyclopentyl-3-ethyl-6-(4-aminophenylmethyl)pyrazolo [3,4-d]pyrimindin-4-one.

WO 96/28448 discloses compounds of the formula



wherein:

R^1 is tert-butyl, or cyclopentyl;

R^3 is lower-alkyl, or phenyl-lower-alkyl; and

R^6 is phenyl, or phenyl substituted by from one to three, the same or different, substituents selected from the group consisting of lower-alkoxy, lower-alkyl, hydroxy, 1-imidazolyl,

lower-alkenyloxy, dilower-alkylamino-lower-alkoxy, 4-morpholinyl-lower-alkoxy, lower-alkoxycarbonyl-lower-alkoxy, carboxylower-alkoxy, trifluoromethyl, 1-piperidinyl-lower-alkoxy, 1-pyrrolidinyl-lower-alkoxy, nitro, halo, amino, $-(CH_2)_2O-$, lower-alkylsulfonylamino, lower-alkoxy-lower-alkoxy, lower-alkenyl, dilower-alkylamino, $-OCH(CH_3)CH_2-$, 4-morpholinylcarbonyl-lower-alkoxy, 4-thiomorpholinyl-lower-alkoxy, pyridinyl-lower-alkoxy, 1-lower-alkyl-3-hexahydroazepinyloxy, and 1-lower-alkyl-4-piperidinyl oxy; or a pharmaceutically acceptable acid-addition salt and/or hydrate thereof.

Preferred compounds include:

1- cyclopentyl-3-ethyl-6-(2-propoxyphenyl)pyrazolo[3,4-d] pyrimindin-4-one,

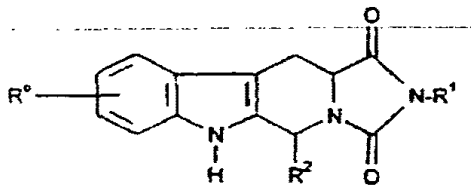
1-cyclopentyl-3-ethyl-6-[4-(1-imidazolyl)phenyl]pyrazolo [3,4-d]pyrimindin-4-one,

1-cyclopentyl-3-ethyl-6-[3-(2-(4-morpholinyl)ethoxy) phenyl]pyrazolo[3,4-d]pyrimindin-4-one,

1-cyclopentyl-3-ethyl-6-[2-ethoxy-4-(1-imidazolyl)phenyl] pyrazolo[3,4-d]pyrimindin-4-one, and

1-cyclopentyl-3-ethyl-6-[2-(CH_2=$CHCH_2O$)phenyl]pyrazolo [3,4-d] pyrimindin-4-one.

WO 96/32003 discloses compounds of the formula



(I)

and salts and solvates thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 is selected from the group consisting of:

(a) hydrogen;

(b) C_{1-6}alkyl optionally substituted by one or more substituents selected from phenyl, halogen, $-CO_2R^a$ and $-NR^aR^b$;

(c) C_{3-6}cycloalkyl;

(d) phenyl; and

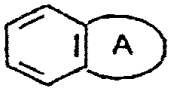
(e) a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from oxygen, nitrogen and sulphur, and being optionally substituted by one or more C_{1-6}alkyl, and optionally linked to the nitrogen atom to which R^1 is attached via C_{1-6}alkyl;

R^2 is selected from the group consisting of:

(f) C_{3-6}cycloalkyl;

(g) phenyl optionally substituted by one or more substituents selected from $-OR^a$, $-NR^aR^b$, halogen, hydroxy, trifluoromethyl, cyano and nitro;

(h) a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from oxygen, nitrogen and sulphur; and

(i) a bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and A is a 5- or 6-membered heterocyclic ring as defined in point (h); and

R^a and R^b independently represent hydrogen or C_{1-6}alkyl.

Preferred compounds include:

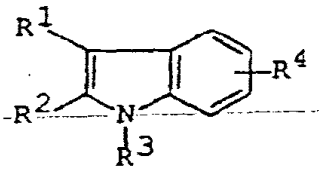
Cis-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-5-(4-methoxyphenyl)-2-methyl-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-ethyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-ethyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-ethyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-ethyl-5-(2-thienyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-dimethylaminophenyl)-2-ethyl-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-9-methyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-9-bromo-2-butyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-9-fluoro-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-9-fluoro-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(3-chlorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(3-chlorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;

Cis-2-butyl-5-(4-chlorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-chlorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-fluorophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;

Trans-2-butyl-5-(4-hydroxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(4-trifluoromethylphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(4-cyanophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-cyanophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(4-nitrophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(4-nitrophenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(3-pyridyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b] indole-1,3(2H)-dione;
Cis-2-butyl-5-(3-thienyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(3-thienyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-butyl-5-(3-furyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-(3-furyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-cyclohexyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-cyclohexyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-cyclohexyl-9-fluoro-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-cyclohexyl-9-fluoro-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Cis-2-benzyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
(5R,11aR)-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-(4-hydroxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;

Trans-2-(2-chloroethyl)-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-2-benzyl-5-cyclohexyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-cyclohexyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-butyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-cyclohexyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Cis-2-cyclohexyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-ethoxycarbonylmethyl-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-2-[2-(2-pyridyl)-ethyl]-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-cyclopropyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans -2-phenethyl-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-5-phenyl-2-(2-pyridylmethyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-5-phenyl-2-(4-pyridylmethyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-2-(3-pyridylmethyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-(2-dimethylamino-ethyl)-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-(3-dimethylamino-propyl)-5-(4-methoxyphenyl)- 5,6,11,11a-tetrahydro -1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-2-(2-morpholin-4-yl-ethyl)-5-phenyl-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-2-[3-(4-methyl-piperazin-1-yl)-propyl]- 5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-2-(2-pyrrolidin-1-yl-ethyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dion;
Trans-5-(4-methoxyphenyl)-2-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-5,6,11,11a-tetrahydro -1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3(2H)-dione;
Trans-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3 (2H)-dione;
Cis-5-(4-methoxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6] pyrido [3,4-b]indole-1,3 (2H)-dione;
and pharmaceutically acceptable salts and solvates thereof.

WO 96/32379 discloses compounds of the formula



(I)

wherein

R^1 is hydrogen, halogen, nitro, carboxy, protected carboxy, acyl, cyano, hydroxyimino(lower)alkyl, lower alkenyl optionally substituted with oxo, or lower alkyl optionally substituted with protected carboxy, carboxy or hydroxy;

R^2 is hydrogen, halogen, lower alkenyl, acyl, or lower alkyl optionally substituted with protected carboxy, carboxy, lower alkoxy or hydroxy;

R^3 is lower alkenyl or lower alkyl, both of which are optionally substituted with one or more substituent(s) selected from the group consisting of

(1) oxo,

(2) aryl optionally substituted with one or more substituent(s) selected from the group consisting of halogen, aryl, lower alkoxy, lower alkylenedioxy, cyano, nitro, carboxy, protected carboxy, acyl, and amino optionally substituted with acyl or protected carboxy, and

(3) a heterocyclic group optionally substituted with halogen; and

R^4 is carboxy, protected carboxy, acyl, cyano, halogen, a heterocyclic group, amino optionally substituted with acyl or protected carboxy, or lower alkyl

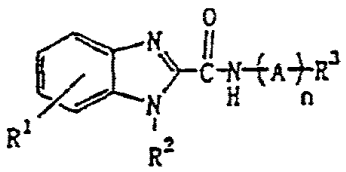
optionally substituted with protected carboxy, carboxy or acyl;

in addition to their significances above,

R^1 and R^2, together with the carbon atoms to which they are attached, represent a 4- to 7-membered carbocyclic ring optionally substituted with oxo,

or its pharmaceutically acceptable salt.

WO 97/03070 discloses compounds of the formula



wherein R^1 is a hydrogen atom or a halogen atom;

R^2 is a phenyl-lower alkyl group;

R^3 is a heterocyclic group selected from the group consisting of an indolyl group, indolinyl group, 1H-indazolyl group, 2(1H)-quinolinonyl group, 3,4-dihydro-2(1H)-quinolinonyl group and 3,4-dihydro-1,4(2H)-benzoxazinyl group, said heterocyclic group may have 1 to 3 substituents selected from the group consisting of:

a group of the formula -B-R^4, (B is a lower alkylene group; R^4 is a 5- to 11-membered saturated or unsaturated heterocyclic group of single ring or binary ring, having 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, oxygen atom and sulfur atom, (said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group and

oxo group) or a group of the formula $-NR^5R^6$ (R^5 and R^6 are each the same or different, and a hydrogen atom, a lower alkyl group, a cycloalkyl group, a pyridyl-carbonyl group, an isoxazolylcarbonyl group which may have 1 to 3 lower alkyl groups as the substituents, a pyrrolylcarbonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group as the substituent; further R^5 and R^6 may form 5- to 6-membered saturated heterocyclic group by combining to each other, together with the adjacent nitrogen atom being bonded thereto, further with or without other nitrogen atom or oxygen atom; said heterocyclic group may have 1 to 3 substituents selected from the group consisting of a hydroxy group and a phenyl group)); a lower alkenyl group; a lower alkoxycarbonyl group; a phenoxy-lower alkyl group which may have cyano group as the substituents; a halogen-substituted lower alkyl group; and a lower alkoxycarbonyl-substituted lower alkyl group;

A is a lower alkylene group; and

n is 0 or 1.

Preferred compounds include:

1-Benzyl-6-chloro-2-{1-[3-(imidazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.

1-Benzyl-6-chloro-2-{1-[3-(N-cyclohexyl-N-methylamino)propyl]indol-5-ylaminocarbonyl}-benzimidazole.

1-Benzyl-6-chloro-2-{1-[3-(pyrazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.

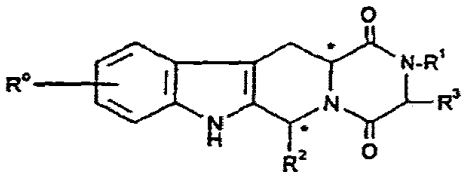
1-Benzyl-6-chloro-2-{1-[3-(1,2,4-triazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.

1-Benzyl-6-chloro-2-{1-[3-(3,5-dimethylisoxazol-4-ylcarbonylamino)propyl]indol-5-ylaminocarbonyl}benzimidazole.

1-Benzyl-6-chloro-2-{1-[3-(4-phenyl-4-hydroxypiperidin-1-yl)propyl]indol-5-ylaminocarbonyl}-benzimidazole.

1-Benzyl-6-chloro-2-{4-[3-(pyridin-2-ylcarbonylamino)propyl]-3,4-dihydro-1,4(2H)-benzoxazin-7-ylaminocarbonyl}benzimidazole.

WO 97/03675 discloses compounds of the formula

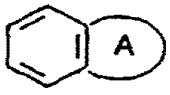


(I)

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

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 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

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl r alkenyl chain;

for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

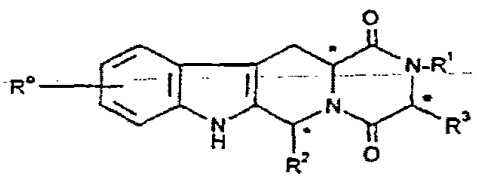
Preferred compounds include:

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[3,4-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;
(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)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
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;
(3S, 6R,12aR)-2,3,6,7,12,12a-hexahydro-3-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.

WO 97/03985 discloses compounds of the formula



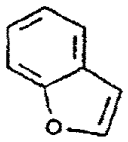
(I)

and solvates thereof, in which:

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen or C_{1-6}alkyl;

R^2 represents the bicyclic ring



which may be optionally substituted by one or more groups selected from halogen and C_{1-3}alkyl;

and

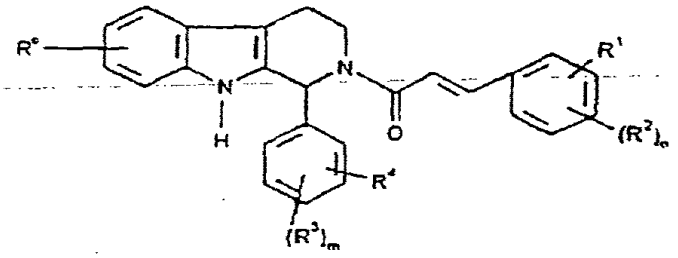
R^3 represents hydrogen or C_{1-3}alkyl.

Preferred compounds include:

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

(3S, 6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2,3-dimethyl-pyrazino[2',1':6,1] pyrido [3,4-b]indole-1,4-dione;
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2-isopropyl-pyrazino [2',1':6,1] pyrido [3,4-b]indole-1,4-dione;
and physiologically acceptable solvates thereof.

WO 97/43287 discloses compounds of the formula



(I)

wherein
R^0 represents -hydrogen or -halogen;
R^1 is selected from the group consisting of:
-hydrogen,
$-NO_2$,
-trifluoromethyl,
-trifluoromethoxy,
-halogen,
-cyano,
a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from oxygen, nitrogen and sulphur (optionally substituted by - C(=0)OR^a or C_{1-4}alkyl),
-C_{1-6}alkyl optionally substituted by -OR^a,
-C_{1-3}alkoxy,
-C(=0)R^a,
-O-C(=0)R^a,
-C(=0)OR^a,
-C_{1-4}alkylene C(=0)OR^a,

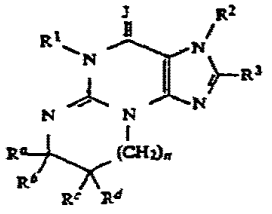
-O-C_{1-4}alkylene -C(=0)OR^a,
-C_{1-4}alkylene-O-C_{1-4}alkylene-C(=0)OR^a,
-C(=0)$NR^aSO_2R^c$,
-C(=0)C_{1-4}alkylene Het, wherein Het represents 5- or 6-membered heterocyclic group as defined above,
-C_{1-4}alkylene NR^aR^b,
-C_{2-6}alkenyleneNR^{a}R^b,
-C(=0)NR^aR^b,
-C(=0)NR^aR^c,
-C(=0)NR^aC_{1-4}alkyl ne OR^b
-C(=0)NR^aC_{1-4}alkylene Het, wher in Het represents a 5- or 6-membered

heterocyclic group as defined above,
-OR^a
-OC_{2-4}alkylene NR^aR^b,
-OC_{1-4}alkylene-$CH(OR^a)CH_2$ NR^aR^b,
-O-C_{1-4}alkylene Het, wherein Het represents a 5- or 6- membered heterocyclic group as defined above,
-O-C_{2-4}alkylene-OR^a,
-O-C_{2-4}alkylene-NR^a-C(=0)-OR^b,
-NR^aR^b,
-NR^aC_{1-4}alkyleneNR$^aR^b$,
-$NR^aC(=0)R^b$,
-$NR^aC(=0)NR^aR^b$,
-$N(SO_2C_{1-4}alkyl)_2$,
-$NR^a(SO_2C_{1-4}alkyl)$,
-$SO_2NR^aR^b$, and
-OSO_2trifluoromethyl;
R^2 is selected from the group consisting of:
-hydrogen,
-halogen,
-OR^a,
-C_{1-6} alkyl,
-NO_2, and
-NR^aR^b,

or R^1 and R^2, together form a 3- or 4- membered alkylene or alkenylene chain, optionally containing at least one heteratom ;
R^3 is selected from the group consisting of:
-hydrogen,
-halogen,
-NO_2,
-trifluoromethoxy,
-C_{1-6}alkyl, and
-$C(=0)OR^a$;
R^4 is hydrogen,
or R^3 and R^4 together form a 3- or 4- membered alkylene or alkenylene chain, optionally containing at least one heteratom;
R^a and R^b, which may be the same or different, are independently selected from hydrogen and C_{1-6}alkyl;
R^c represents phenyl or C_{4-6}cycloalkyl, which phenyl or C_{4-6}cycloalkyl can be optionally substituted by one or more halogen atoms, one or more -$C(=0)OR^a$ or one or more -OR^a;

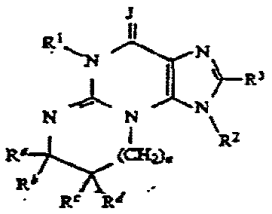
n is an integer selected from 1, 2 and 3;
m is an integer selected from 1 and 2;
and pharmaceutically acceptable salts and solvates thereof.

U.S. Patent No. 5,393,755 discloses compounds of the formula



(I)

or



(I')

wherein
J is oxygen or sulfur,
R^1 is hydrogen, alkyl or alkyl substituted with aryl or hydroxy;
R^2 is hydrogen, aryl, heteroaryl, cycloalkyl, alkyl or alkyl substituted with aryl, heteroaryl, hydroxy, alkoxy, amino, monoalkyl amino or dialkylamino, or $-(CH_2)_mTCOR^{20}$ wherein m is an integer from 1 to 6, T is oxygen or —NH— and R^{20} is hydrogen, aryl, heteroaryl, alkyl or alkyl substituted with aryl or heteroaryl;
R^3 is hydrogen, halo, trifluoromethyl, alkoxy, alkylthio, alkyl, cycloalkyl, aryl, aminosulfonyl, amino, monoalkylamino, dialkylamino, hydroxyalkylamino, aminoalkylamino, carboxy, alkoxycarbonyl or aminocarbonyl or alkyl substituted with aryl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino;
R^a, R^b, R^c and R^d independently represent hydrogen, alkyl, cycloalkyl or aryl; or (R^a and R^b) or (R^c and R^d) or (R^b and R^c) can complete a saturated ring of 5- to 7-carbon atoms, or (R^a and R^b) taken together and (R^b and R^c) taken together, each complete a saturated ring of 5- to 7-carbon atoms, wherein each ring optionally can contain a sulfur or oxygen atom and whose carbon atoms may be optionally substituted with one or more of the following: alkenyl, alkynyl, hydroxy, carboxy, alkoxycarbonyl, alkyl or alkyl substituted with hydroxy, carboxy or alkoxycarbonyl; or such saturated ring can have two adjacent carbon atoms which are shared with an adjoining aryl ring; and
n is zero or one.

Preferred compounds include:

cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4-one;
7,8-Dihydro-5-methyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
5,7,8,9-Tetrahydro-5-methyl-3-(phenylmethyl)-pyrimido[2,1-b]purin-4(3H)-one;
7,8-Dihydro-8-phenyl-5-methyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
5', 7'-Dihydro-5'-methyl-3'-(phenylmethyl)spiro[cyclohexane-1,8'-(8H)imidazo[2,1-b]purin]-4'(3'H)-one;
cis-5,6a,11,11a-Tetrahydro-5-methyl-3-(phenylmethyl-)indeno[1',2':4,5]imidazo[2,1-b]purin-4(3H)-one;
5',7'-Dihydro-2',5'dimethyl-3'-(phenylmethyl)spiro{cyclohexane-1,7'(8'H)-imidazo[2,1-b]purin}-4'-(3'H)-one;
7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
cis-5,6a,7,11b-Tetrahydro-5-methyl-3-(phenylmethyl-)indeno[2',1',:4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4-(3H)-one;
5'-Methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'-(8'H)-(3'H)imidazo[2,1-b]purin]-4-(5'H)-one;
7,8-Dihydro-2,5,7,7-tetramethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5'H)-one;
7,8-Dihydro-7(R)-phenyl-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-3,7(R)-bis(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
(±)-7,8-Dihydro-2,5-dimethyl-7-ethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
6a(S)-7,8,9,10,10a(R)-Hexhydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
6a(R)-7,8,9,10,10a(S)-hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-isopropyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7(R)-trimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
cis-7,7a,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H-cyclopenta[5,6]pyrimido[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-(2-methylpropyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R,S)-(methoxycarbonyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(R,S)-(1-propyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-dimethyl-7(S)-(1-methylethyl)-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7,7,8(R,S)-pentamethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
5,7,8,9-Tetrahydro-2,5,7,9(R,S)-pentamethyl-3-(phenylmethyl)-pyrimido[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(S),7,8,9,9a(R)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-6a,7,8,9,10,10a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)-3H -benzimidazo[2,1-b]purin-4(5H)-one;

5',7'-Dihydro-2',5'-dimethyl-3'-(phenylmethyl)spiro[cyclohexane-1,8-(8H)-imidazo[2,1-b]purin]-4-(3'H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclohept[6,7]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4-(5H)-one;

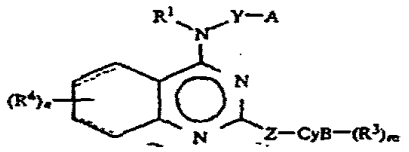
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-ethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-6a,7,8,9,10,10a-Hexahydro-5-methyl-2-phenyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methylcyclopenta[4,-5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopenta[4,-5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a(R), 7,8,9,9a(S)-Hexahydro-2,5-di-methylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
2',5'-dimethyl-spiro{cyclopentane-1,7'-(8'H)-(3'H)-imidazo[2,1-b]purin}-4'(5'H)-one;
7,8-Dihydro-2,5-dimethyl-7(R)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5,7,7-tetramethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
7,8-Dihydro-2,5-di methyl-7(S)-(1-methylethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
6a(R),7,8,9,10,10a(S)-Hexahydro-2,5-dimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one;
5',7'-Dihydro-2',5'-dimethylspiro{cyclohexane-1,7-(8'H)-imidazo[2,1-b]purin}-4'(3'H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(phenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3H)-thione;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-thione;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(4-chlorophenylmethyl)cyclopenta[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(cyclohexylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(2-naphthylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-bromophenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R)-7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-methoxyphenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,3,5-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(hydroxymethyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2-methylthio-5-methyl-3-(Phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-2-carboxylic acid;
cis-3,4,5,6a,7,8,9,9a-Octahydro-5-methyl-4-oxo-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-2-

carboxylic acid, methyl ester;
cis-5,6a,7,8,9,9a-Hexahydro-2-bromo-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(methylaminosulfonyl)-5-methyl-3-(phenylmethyl)cyclopent[4,-5]imidazo[2,1-b]purin-4(3H)one;
cis-1-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-b]purin-4-(1H)one;
cis-5,6a,7,8,9,9a-Hexahydro-3,5-bis-(phenylmethyl)cyclopent(4,5)imidazo(2,1-b)purin-4(3H)one;
cis-6a,7,8,9,10,10a-Hexahydro-3,5-bis-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)one;
cis-3-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo(2,1-b)purin-4(3H)one;
5'-Methyl-3'-(phenylmethyl)spiro[cyclopentane-1,7-(8'H)-(3'H)imidazo[2,1-b]purin]-4-(5H)one;
2',5'-Dimethyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7-(8'H)-(3H)imidazo[2,1-b]purin]-4-(5'H)one;
cis-5,6a,(R)7,8,9,9a(S)-Hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo(2,1-b)purin-4(3H)one;
cis-3-Cyclopentyl-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
5'-Methyl-2'-trifluoromethyl-3'-(phenylmethyl)spiro{cyclo-pentane-1,7'(8'H)-(3'H)imidazo[2,1-b]purin}-4-(5'H)-one;
7,8-Dihydro-5,7,7-trimethyl-2-trifluoromethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(5H)-one;
(+/−)-cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-trifluoromethyl-3-(phenylmethyl)cyclopent[4,-5]imidazo[2,1-b]purin-4(3H)-one;
(+/−)-6a,7,8,9,9a,10,11,11 a-Octahydro-2,5-dimethyl-3-(phenylmethyl)-3H-pentaleno[6a',1':4,-5]imidazo[2,1-b]purin-4(5H)-one;
(+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
(−)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3-phenylmethyl-3H-pentaleno[6a',1':4,5]Imidazo[2,1-b]purin-4(5H)-one;
(+/−) 6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
(+)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
(−)-6a,7,8,9,9a,10,11,11a-Octahydro-2,5-dimethyl-3H-pentaleno[6a',1':4,5]imidazo[2,1-b]purin-4(5H)-one;
6a,7,8,9,10,10a,11,12,13,13a-Decahydro-2,5-dimethyl-(3-phenylmethyl)napth[1,8a-d]imidazo[2,1-b]purin-4(5H)one;
7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;
7(R)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3-(phenylmethyl)-3H-imidazo[2,1-b]purin-4(3H)-one;
7(S)-Cyclohexyl-7,8-dihydro-2,5-dimethyl-3H-imidazo[2,1-b]purin-4(5H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(trimethylacetoxy)methyl]-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-pyridylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[2-(1-morpholinyl)ethyl]cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-[acetoxymethyl]cyclopent[4,5]imidazo[2.1-b]purin-4(3H)-one;
5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenyimethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R),7(S),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;

5,6a(S),7(R),8,9,9a-Hexahydro-2,5,6a-trimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
cis-6a,7,8,9, 10,10a-Hexahydro-2,5,7-trimethyl-3-(phenylmethyl)-3H-benzimidazo[2,1-b]purin-4(5H)-one;
cis-5,6a,7,8,9,9a-Hexahydro-2,5,6a-trimethylcyclopent[4,5]imidazo[2,1-b]purin-4(3H); or
cis-6a,7,8,9,10,10a-Hexahydro-2,5,7-trimethyl-3H-benzimidazo[2,1-b]purin-4(5H)-one].

U.S. Patent No. 5,439,895 discloses compounds of the formula


(I)

wherein R^1 is hydrogen or C1–4 alkyl;
Y is C1–6 alkylene;
A is —O—R^0 or —S(O)p—R^0,
in which R^0 is C1–4 alkyl-hydroxy;
p is 0–2;
Z is single bond, methylene, ethylene, vinylene or ethynylene;
CyB is
(1) 7-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one, two or three nitrogen atoms,
(2) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, two or three nitrogen atoms,
(3) 6-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atom, one nitrogen atom,
(4) 4- or 5-membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one, two or three nitrogen atoms, or
(5) 4–7 membered, unsaturated or partially saturated, monocyclic hetero ring containing as hetero atoms, one or two oxygen atoms, or one or two sulfur atoms;
R^3 is hydrogen, C1–4 alkyl, C1–4 alkoxy, halogen or trifluoromethyl;
R^4 is (1) hydrogen, (2) C1–4 alkyl, (3) C1–4 alkoxy, (4) —COOR^8, in which R^8 is hydrogen or C1–4 alkyl, (5) —NR^9R^{10}, in which R^9 is hydrogen, C1–4 alkyl or phenyl(C1–4 alkyl) and R^{10} is hydrogen or C1–4 alkyl, (6) —NHCOR^{11}, in which R^{11} is C1–4 alkyl, (7) —NHSO_2R^{11}, in which R^{11} is as hereinbefore defined, (8) SO_2NR^9R^{10}, in which R^9 and R^{10} are as hereinbefore defined, (9) —OCOR^{11}, in which R^{11} is as hereinbefore defined, (10) halogen, (11) trifluoromethyl, (12) hydroxy, (13) nitro,

(14) cyano, (15) $-SO_2N{=}CHNR^{12}R^{13}$ in which R^{12} is hydrogen or C1–4 alkyl and R^{13} is C1–4 alkyl, (16) $-CONR^{14}R^{15}$ in which R^{14} is hydrogen or C1–4 alkyl and R^{15} is C1–4 alkyl or phenyl(C1–4 alkyl), (17) C1–4 alkylthio, (18) C1–4 alkylsulfinyl, (19) C1–4 alkylsulfonyl, (20) ethynyl, (21) hydroxymethyl, (22) tri(C1–4 alkyl)silylethynyl or (23) acetyl; and m and n independently are 1 or 2; with the proviso that

(1) a CyB ring does not bond to Z through a nitrogen atom in the CyB ring when Z is vinylene or ethynylene;

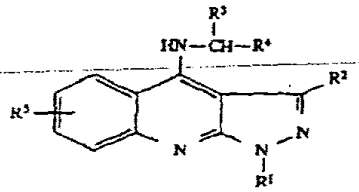
or pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

Preferred compounds include:

4-[2-(2-hydroxyethoxy)ethyl]amino-6-acetyl-2-(1-imidazolyl)quinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-ethynylquinazoline,
2-(1-imidazolyl)-4-[2-(2-hydroxyethoxy)ethyl]amino-6-(2-triisopropylsilylethynyl)quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-hydroxymethyl-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylsulfinyl-2-(1-imidazolyl)quinazoline,
6-chloro-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,
4-[2-(2-hydroxyethoxy)ethyl]amino-6-methoxycarbonyl-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-methylthio-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-6-iodo-2-(1-imidazolyl)quinazoline,
4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)-5,6,7,8-tetrahydroquinazoline or
6-methoxy-4-(2-(2-hydroxyethoxy)ethyl)amino-2-(1-imidazolyl)quinazoline,

and pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

U.S. Patent No. 5,488,055 discloses compounds of the formula



wherein:

R^1 is lower-alkyl, phenyl-lower-alkyl, or cycloalkyl;

R^2 is hydrogen, or lower-alkyl;

R^3 is hydrogen, lower-alkyl, or hydroxylower-alkyl;

R^4 is cycloalkyl or cylcoalkyl substituted by from one to two, the same or different, substituents selected from the group consisting of lower-alkoxycarbonyl, carboxy, lower-alkylthio-lower-alkoxycarbonyl, hydroxylower-alkyl, hydroxy, oxo, lower-alkoxy, lower-alkyl, and halogen; and

R^5 is from one to three, the same or different, substituents selected from the group consisting of hydrogen, lower-alkoxy, hydroxy, dilower-alkylamino-lower-alkoxy, carboxylower-alkoxy, lower-alkoxycarbonyl-lower-alkoxy, nitro, polyhydroxylower-alkoxy, amino, epoxy-lower-alkoxy, carboxy, lower-alkanoylamino, lower-alkoxycarbonyl, pyridinyl, 4-morpholinyl-lower-alkoxy, lower-alkylsulfonyl, cyano, 1-imidazolyl, halogen, dilower-alkylaminosulfonyl, oxadiazolyl (or oxadiazolyl substituted on any available carbon atom thereof by lower-alkyl), lower-alkylsulfinyl, 1-pyrazolyl (or 1-pyrazolyl substituted on any available carbon atom thereof by lower-alkyl), trifluoromethylsulfonyl, lower-alkenyl, lower-alkyl, and lower-alkynyl; or a pharmaceutically acceptable acid-addition salt and/or hydrate and/or solvate thereof, or, where applicable, a stereoisomer or a racemic mixture thereof.

Preferred compounds include

1-ethyl-6-nitro-*N*-[*S*(+)-1-(cyclohexyl) ethyl]-1H-pyrazolo [3,4-b]quinolin-4-amine,

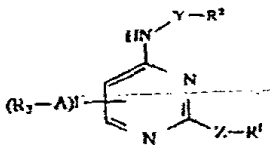
1-ethyl -6-nitro-*N*-[cyclohexylmethyl]- 1H-pyrazolo [3,4-b]quinolin-4-amine,

1-ethyl-6-cyano-*N*-[*S*(+)-1-(cyclohexyl)ethyl]-1H-pyrazolo [3,4-b]quinolin-4-amine,

1-ethyl-6-bromo-*N*-[*S*(+)-1-(cyclohexyl)ethyl]-1H-pyrazolo [3,4-b]quinolin-4-amine, and

1-ethyl-6-(1-pyrazolyl)-*N*-[*S*(+)-1-(cyclohexyl)ethyl]-1H-pyrazolo [3,4-b]quinolin-4-amine.

U.S. Patent No. 5,525,064 discloses compounds of the formula



(I)

wherein A is a bond, C_{1-4} alkylene or C_{1-4} oxyalkylene;

Y is a bond, C_{1-4} alkylene, C_{1-4} alkyleneoxy, C_{1-4} alkoxyphenylene or phenyl(C_{1-4})alkylene;

Z is a bond or vinylene;

R^1 is a heterocyclic ring selected from the group consisting of pyrrole, pyridine, azepine, imidazole, pyrazole, pyrimidine, pyrazine, pyridazine, benzimidazole, quinoline, isoquinoline and partially or fully saturated rings thereof;

R^2 is

(i) a heterocyclic ring selected from the group consisting of pyrrole, pyridine, azepine, imidazole, pyrazole, pyrimidine, pyrazine, pyridazine, benzimidazole, quinoline, isoquinoline, furan, pyran, dioxole, dioxine, benzofuran, benzopyran, benzodioxole, benzodioxine, thiophene, thioine, benzothiophene, benzothione and partially or fully saturated rings thereof,

(ii) C_{4-15} carbocyclic ring,

(iii) C_{1-4} alkoxy,

(iv) hydroxy(C_{1-4} alkoxy), or

(v) hydroxy;

with the proviso that:

when R^1 is pyridine or pyridine substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl or nitro then R^2 is a member selected only from the group consisting of benzodioxole or benzodioxole substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl, nitro or a group of the formula:

$$-COOR^{10}$$

wherein R^{10} is hydrogen or C_{1-4} alkyl, and hydroxy(C_{1-4} alkoxy);

R^3 is

(i) a heterocyclic ring selected from the group consisting of pyrrole, pyridine, azepine, imidazole, pyrazole, pyrimidine, pyrazine, pyridazine, benzimidazole, quinoline, isoquinoline, furan, pyran, benzofuran, benzopyran, thiophene, thioine, benzothiophene, benzothione, thiazole, isothiazole, thiazine, benzothiazole, benzoisothiazole, benzothiazine and partially or fully saturated rings thereof,

(ii) C_{4-15} carbocyclic ring,

(iii) a group of formula:

$$CH_2{=}CH(X)-$$

wherein X is halogen, or

(iv) hydrogen,

l is 1 or 2,

with the proviso that:

the ring represented by R^1 may be substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl or nitro;

the ring represented by R^2 may be substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl, nitro or a group of the formula:

—$COOR^{10}$

wherein R^{10} is hydrogen or C_{1-4} alkyl, and the ring represented by R^3 may be substituted by one or two of C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl, nitro, cyano, ethynyl or a group of the formula:

—$SONR^7R^8$

wherein R^7 and R^8 are independently hydrogen or C_{1-4} alkyl, and with the proviso that:

R^2 is not hydroxy when Y is a bond; and

R^1 is not bonded through its nitrogen atom when Z is vinylene,

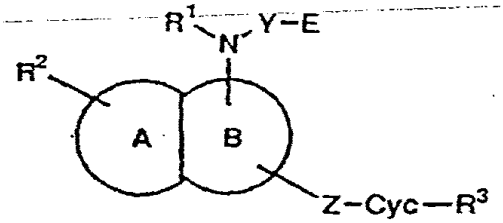
or pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable salts thereof.

Preferred compounds include

2-(1-Imidazolyl)-4-[2-(2-hydroxyethoxy)ethylamino-5-(3-methoxyphenyl)methylpyrimidine,
2-(1-Imidazolyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-4-(2-methoxyethyl)aminopyrimidine,
2-(1-Imidazolyl)-5-ethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-phenylmethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-methyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5,6-dimethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-methoxyphenyl)methyl-4-(2-methoxyethyl)aminopyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-[2-(2-hydroxyethoxy)ethyl]aminopyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-(2-methoxyethyl)aminopyrimidine or
2-(1-Imidazolyl)-5-(4-methoxyphenyl)methyl-4-phenylmethylaminopyrimidine.
2-(1-Imidazolyl)-5-phenoxymethyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(1-Imidazolyl)methyl-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(1-chlorovinyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thiazolyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-[2-(2-hydroxyethoxy)ethyl]aminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1-naphthyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-methoxyphenyl)methylaminopyrimidine,

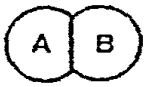
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-methoxyphenyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-furyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-thienyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-pyridyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-methoxyethyl)aminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-phenylmethoxyaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-chlorophenyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-chlorophenyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-methylphenyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-methoxyphenyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(5-methyl-2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-[4-(1-imidazolyl)phenyl] methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-pyridyl)-4-(1,3-dioxaindan- 5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-furyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(3-pyridyl)-4-phenylmethylaminopyrimidine,
2-(1-Imidazolyl)-5-(4-chlorophenyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(Benzimidazol-1-yl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(4-ethoxycarbonylphenyl-)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-naphthyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(3-Pyridyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-[2-(3-Pyridyl)vinyl]-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine,
2-(2-Methyl-1-Imidazolyl)-5-(2-thienyl)-4-(1,3-dioxaindan-5-yl)methylaminopyrimidine or
2-(1-Imidazolyl)-5-(2-thienyl)-4-(benzimidazol-5-yl)methylaminopyrimidine.

European published patent application No. 0728759 discloses compounds of the formula

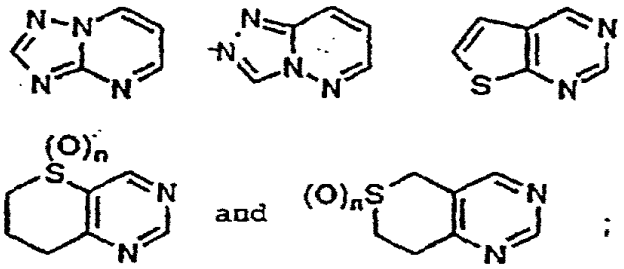


(I)

wherein



is a heterocycle selected from



;

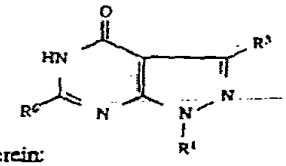
n is 0, 1 or 2;
Y is single bond or C1-6 alkylene;
Z is single bond, C1-2 alkylene or vinylene;
E is

(i) 4-15 membered, unsaturated, partially saturated or fully saturated, mono or bicyclic hetero ring containing one or two hetero atoms, chosen from nitrogen, oxygen and sulfur, not more than one hetero atom being sulfur,
(ii) 4-15 membered, unsaturated or partially saturated, mono or bicyclic carbocyclic ring, or
(iii) $-OR^4$; in which R^4 is hydrogen atom, C1-4 alkyl or C1-4 alkyl substituted by a hydroxy group;

Cyc is 5-7 membered, unsaturated, partially saturated or fully saturated, monocyclic hetero ring containing one or two nitrogen atoms or 5-7 membered, unsaturated or partially saturated, monocyclic carbocyclic ring;
R^1 is hydrogen atom or C1-4 alkyl;
R^2 is hydrogen atom, C1-4 alkyl, C1-4 alkoxy or halogen atom;
R^3 is hydrogen atom, C1-4 alkyl, C1-4 alkoxy or $-COOR^5$; in which R^5 is hydrogen atom or C1-4 alkyl;
with the proviso that

(1) a Cyc ring does not bond to Z through a nitrogen atom in the Cyc ring where Z is vinylene and that
(2) Y is not a single bond, when E is $-OR^4$; or a pharmaceutically acceptable acid addition salt, pharmaceutically acceptable salt or hydrate thereof.

U.S. Patent No. 5,541,187 discloses compounds of the formula



wherein:

R^1 is hydrogen, alkyl, cycloalkyl, cycloalkyl substituted by alkyl or hydroxyl, 2- or 3-tetrahydrofuranyl, 3-tetrahydrothienyl 1,1,-dioxide, cycloalkyl-alkyl, carboxy-alkyl, carbo-lower-alkoxy-alkyl, dialkylaminoalkyl, phenyl-lower-alkyl, phenyl-lower-alkyl in which the phenyl ring is substituted in the 2, 3, or 4-position by one or two substituents, the same or different, selected from the group consisting of amino, halogen, alkyl, carboxyl, carbo-lower-alkoxy, carbamoyl, $NHSO_2$-(quinolinyl), nitro and cyano;

R^3 is hydrogen, lower-alkyl, phenyl-lower-alkyl, lower-alkoxyphenyl-lower-alkyl, dilower-alkoxy-phenyl-lower-alkyl, pyridyl-lower-alkyl, cycloalkyl-lower-alkyl, phenylamino, dialkylamino, halogen, trifluoromethyl, lower-alkylthio, cyano or nitro; and

R^6 is a five or six membered heterocyclic ring containing from one to two nitrogen atoms, substituted—or unsubstituted—at any available carbon atom by one or two substituents, the same or different, selected from the group consisting of lower-alkyl, halogen, lower-alkoxy, cycloalkyloxy, 4-morpholinyl,. lower-alkoxy-lower-alkoxy, hydroxy, imidazolyl, oxo and 4-morpholinyl-lower-alkoxy; or at any available nitrogen atom by lower-alkyl, lower-alkanoyl, or trifluoroacetyl; or a pharmaceutically acceptable acid-addition salt thereof.

Preferred compounds include:

1-Cyclopentyl-3-methyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

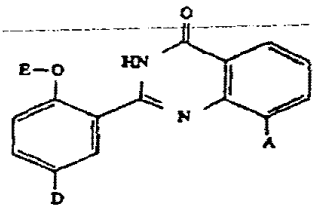
1-Cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

1-Cyclopentyl-3-ethyl-6-(3-methoxy-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

1-Cyclopentyl-3-trifluoromethyl-6-(3-ethoxy-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

1-Cyclopentyl-3-ethyl-6-(2-(1-imidazolyl)-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

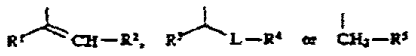
U.S. Patent No. 5,721,238 discloses compounds of the formula



(I)

in which

A represents oxiranyl, which is optionally substituted by straight-chain or branched alkyl having up to 8 carbon atoms, which in turn can be substituted by phenyl, or represents a radical of the formula



wherein

R^1 denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

R^2 denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by phenyl,

R^3 denotes straight-chain or branched alkyl having up to 5 carbon atoms or a group of the formula $-OR^6$,

wherein

R^6 denotes hydrogen, a hydroxyl-protecting group or straight-chain or branched alkyl having up to 5 carbon atoms,

R^4 denotes straight-chain or branched alkyl having 2 to 10 carbon atoms, which is optionally substituted by phenyl,

L denotes a radical of the formula —CO—, —CH(OH), $-CH_2$, $-CH(N_3)$ or $-CH(OSO_2R^7)$,

wherein

R^7 denotes straight-chain or branched alkyl having up to 4 carbon atoms or phenyl,

R^5 denotes straight-chain or branched alkyl having 3 to 8 carbon atoms which is substituted by phenyl, or denotes benzyl or 2-phenylethyl,

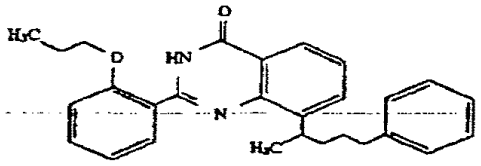
D represents hydrogen, or represents a group of the formula $-SO_2-NR^8R^9$,

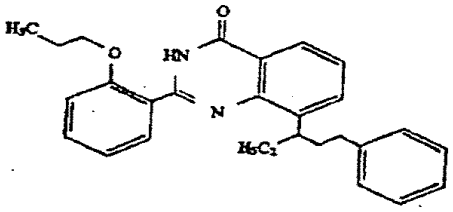
wherein

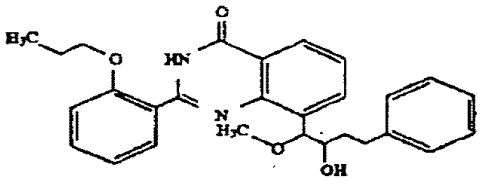
R^8 and R^9 are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, or, together with the nitrogen atom, form a 5- to 6-membered saturated heterocyclic radical which has up to 2 further hetero atoms from the series consisting of S, N and/or O and is optionally substituted, including via a free N function, by straight-chain or branched alkyl having up to 6 carbon atoms, which in turn can be substituted by hydroxyl, and

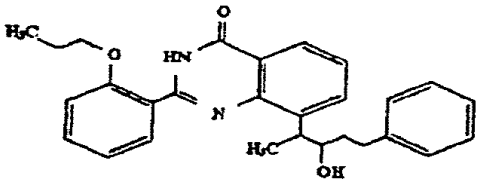
E represents straight-chain or branched alkyl having up to 8 carbon atoms, and tautomers and salts thereof.

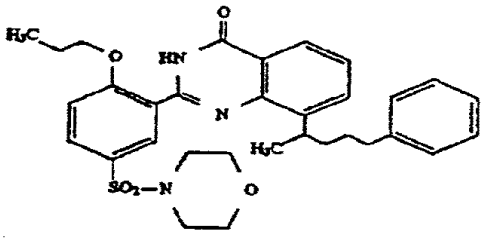
Preferred compounds include:

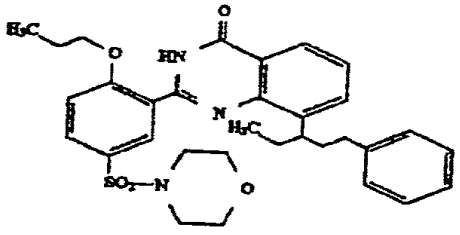




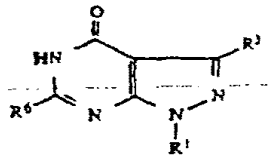








U.S. Patent No. 5,294,612 discloses compounds of the formula



wherein:

R^1 is hydrogen, alkyl, C_4 to C_7 cycloalkyl, C_4 to C_7 cycloalkyl substituted by C_1 to C_{10} alkyl or hydroxyl, 2- or 3-tetrahydrofuranyl, 3-tetrahydrothienyl 1,1, -dioxide, C_4 to C_7 cycloalkyl-C_1 to C_{10} alkyl, carboxy-C_1 to C_{10} alkyl, carbo-C_1 to C_4 lower-alkoxy-C_1 to C_{10} alkyl, dialkylamino C_1 to C_{10} alkyl, phenyl-C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl in which the phenyl ring is substituted in the 2, 3, or 4-position by one or two substituents, the same or different, selected from the group consisting of amino, halogen, C_1 to C_{10} alkyl, carboxyl, carbo-C_1 to C_4 lower-alkoxy, carbamoyl, $NHSO_2$-(quinolinyl), nitro and cyano;

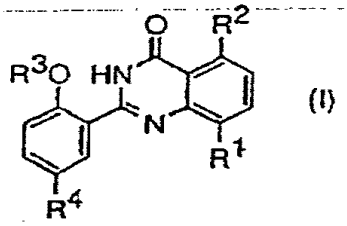
R^3 is, C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl, lower-alkoxyphenyl-C_1 to C_4 lower-alkyl, diC_1 to C_4 lower-alkoxy-phenyl-C_1 to C_4 lower-alkyl, pyridyl-C_1 to C_4 lower-alkyl, C_4 to C_7 cycloalkyl-C_1 to C_4 lower-alkyl, phenylamino, diC_1 to C_{10} alkylamino, halogen, trifluoromethyl, C_1 to C_4 lower-alkylthio, cyano or nitro; and

R^6 is a nine or ten membered bicyclic ring having carbon and from one to two nitrogen atoms, and the heterocycle is made up of fused 5 or 6 membered rings or such ring substituted at any available carbon atom by one or two substituents, the same or different, selected from the group consisting of C_1 to C_4 lower-alkyl, halogen, C_1 to C_4 lower-alkoxy, C_4 to C_7 cycloalkyloxy, 4-morpholinyl, C_1 to C_4 lower-alkoxy-C_1 to C_4 lower-alkoxy, hydroxy, imidazolyl, oxo and 4-morpholinyl-C_1 to C_4 lower-alkoxy, or at any available nitrogen atom by C_1 to C_4 lower-alkyl, C_2 to C_4 lower-alkanoyl, or trifluoroacetyl; or a pharmaceutically acceptable acid-addition salt thereof.

Preferred compounds include:

1-Cyclopentyl-3-methyl-6-(4-quinolinyl)-pyrazolo[3,4-d]pyrimidin-4-one

WO 93/12095 discloses compounds of the formula



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is H, C_1-C_4 alkyl, C_1-C_4 alkoxy or $CONR^5R^6$;

R^2 is H or C_1-C_4 alkyl;

R^3 is C_2-C_4 alkyl;

R^4 is H, C_2-C_4 alkanoyl optionally substituted with NR^7R^8, (hydroxy)C_2-C_4 alkyl optionally substituted with NR^7R^8, $CH=CHCO_2R^9$, $CH=CHCONR^7R^8$, $CH_2CH_2CO_2R^9$, $CH_2CH_2CONR^7R^8$, $SO_2NR^7R^8$, $SO_2NH(CH_2)_nNR^7R^8$ or imidazolyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl;

R^7 and R^8 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino or 4-(NR^{10})-1-piperazinyl group wherein any of said groups is optionally substituted with $CONR^5R^6$;

R^9 is H or C_1-C_4 alkyl;

R^{10} is H, C_1-C_3 alkyl or (hydroxy)C_2-C_3 alkyl;

and n is 2, 3 or 4;

with the proviso that R^4 is not H when R^1 is H, C_1-C_4 alkyl or C_1-C_4 alkoxy.

Preferred compounds include:

2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-methylquinazolin-4-(3H)-one;

2-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-8-methylquinazolin-4(3H)-one;

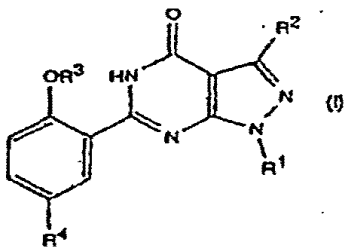
8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one;

8-carbamoyl-2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}quinazolin-4(3H)-one;

and 8-ethylcarbamoyl-2-(2-n-propoxyphenyl)quinazolin-4(3H)-one;

and pharmaceutically acceptable salts thereof.

WO 93/07149 discloses compounds of the formula



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is C_1-C_6 alkyl;

R^2 is H, methyl or ethyl;

R^3 is C_2-C_4 alkyl;

R^4 is C_1-C_8 alkyl optionally substituted with NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; $SO_2NR^5R^6$; $CONR^5R^6$; CO_2R^7; or halo;

R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl group wherein said group is optionally substituted by one or two C_1-C_4 alkyl groups;

R^7 is H or C_1-C_4 alkyl;

and R^8 is H, C_1-C_3 alkyl or hydroxy C_2-C_3 alkyl.

Preferred compounds include:

6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

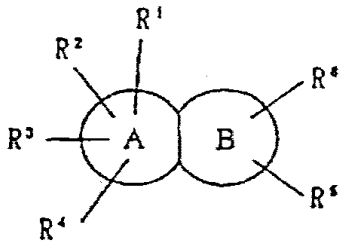
6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

and 3-methyl-6-[5-(2-morpholinocarbonylethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

and pharmaceutically acceptable salts thereof.

European published patent application No. 0607439 discloses compounds of the formula

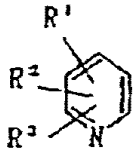


(1)

[in formula (1), ring A represents a benzene ring, a pyridine ring or a cyclohexane ring; ring B represents a pyridine ring, a pyrimidine ring, or an imidazole ring.

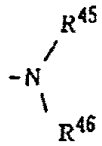
Provided that the ring A and the ring B are combined sharing two atoms and the atoms shared may be either a carbon atom or a nitrogen atom.

In the case where the ring A is a pyridine ring and that except the case where the ring B shares the nitrogen atom of this pyridine ring to combine therewith, the ring A is represented by



R^1, R^2, R^3 and R^4, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a lower alkyl group which may be substituted with a halogen atom, a cycloalkyl group which may be substituted, a lower alkoxy group, a hydroxyalkyl group, a nitro group, a cyano group, an acylamino group, a carboxyl group which may be protected, a group represented by the formula

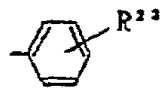
(wherein R^7 represents a lower alkyl group, and n represents 0 or an integer of 1 to 2), or a group represented by the formula



(wherein R^{45} and R^{46}, each of which may be the same or different from each other, represent each a hydrogen atom or a lower alkyl group; or R^{45} and R^{46} can form a ring which may contain another nitrogen atom or oxygen atom together with the nitrogen atom to which they are bonded with the proviso that this ring may be substituted); or, two of R^1, R^2, R^3 and R^4 may together form methylenedioxy, ethylenedioxy or a phenyl ring.

R^5 represents a hydrogen atom, a halogen atom, a hydroxyl group, a hydrazino group, a lower alkyl group, a cycloalkyl group which may be substituted, a lower alkoxy group, a lower alkenyl group, a carboxyalkyl group which may be protected, a carboxyalkenyl group which may be protected, a hydroxyalkyl group, a carboxyl group which may be protected, a group represented by the formula

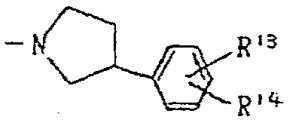
(wherein R^8 represents a lower alkyl group, and m represents 0 or an integer of 1 to 2), a group represented by the formula $-O-R^9$ (wherein R^9 represents a hydroxyalkyl group which may be protected, a carboxyalkyl group which may be protected or a benzyl group which may be substituted), a group represented by the formula



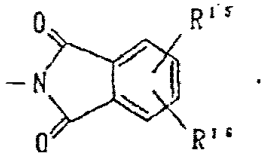
(wherein R^{23} represents a hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group or a hydroxyalkyloxy group), a heteroaryl group which may be substituted, a 1,3-benzdioxolyl group which may be substituted, a 1,4-benzdioxyl group which may be substituted, a 1,3-benzdioxolylalkyl group which may be substituted, a 1,4-benzdioxylalkyl group which may be substituted, a group represented by the formula $-C(R^{24})=X$ [wherein X represents an oxygen atom, a sulfur atom or a group represented by the formula $=N-R^{10}$ (wherein R^{10} represents a hydroxyl group, a cyano group or a carboxyalkyloxy group which may be protected); and R^{24} represents a hydrogen atom or a lower alkyl group], or a group represented by the formula $-NR^{11}R^{12}$ (wherein R^{11} and R^{12}, each of which may

be the same or different from each other, represent each a hydrogen atom, a lower alkyl group, a hydroxyalkyl group, an aminoalkyl group, a carboxyalkyl group which may be protected, an alkylcarbamoyl group, a carboxyalkylcarbamoyl group which may be protected, a heteroarylalkyl group which may be substituted, a 1,3-benzoxolylalkyl group or a 1,4-benzdioxylalkyl group; or, further, R^{11} and R^{12} can form a ring which may contain another nitrogen atom or oxygen atom together with a nitrogen atom to which they are bonded with the proviso that this ring may be substituted).

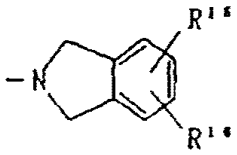
R^6 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a lower alkyl group, a lower alkoxy group, a lower alkenyl group, a 1,3-benzdioxolylalkyloxy group, a 1,4-benzdioxylalkyloxy group, a phenylalkyloxy group which may be substituted, a group represented by the formula



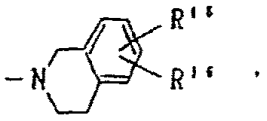
(wherein R^{13} and R^{14}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{13} and R^{14} may together form methylenedioxy or ethylenedioxy), a group represented by the formula



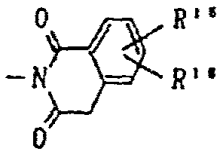
a group represented by the formula



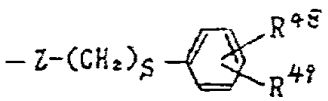
a group represented by the formula



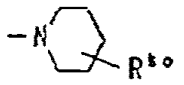
a group represented by the formula



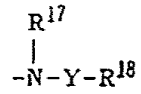
(in these formulas, R^{15} and R^{16}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{15} and R^{16} may together form methylenedioxy or ethylenedioxy), a piperidine-4-spiro-2'-dioxan-1-yl group, a group represented by the formula



(wherein R^{48} and R^{49}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{48} and R^{49} may together form methylenedioxy or ethylenedioxy; and Z represents a sulfur atom or an oxygen atom), a group represented by the formula

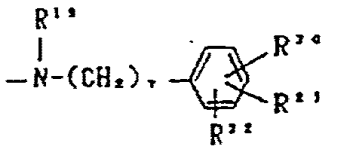


(wherein R^{50} represents a hydroxyl group, a halogen atom, a lower alkyl group, a lower alkoxy group, a carboxyl group which may be protected, a cyano group, a hydroxyalkyl group or a carboxyalkyl group), a group represented by the formula



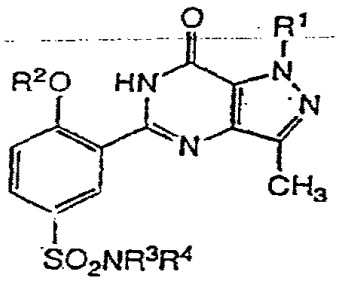
[wherein R^{17} represents a hydrogen atom, a lower alkyl group, an acyl group, a lower alkoxyalkyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; Y represents a group represented by the formula $-(CH_2)_q-$ (wherein q is 0 or an integer of 1 to 8), or a group represented by the formula

further, in the group represented by the formula $-(CH_2)_q-$, when q is an integer of 1 to 8, each carbon atom may have 1 to 2 substituent(s); and R^{18} represents a hydrogen atom, a hydroxyl group, a carboxyl group which may be protected, a cyano group, an acyl group, a heteroaryl group which may be substituted or a cycloalkyl group which may be substituted], or a group represented by the formula



(wherein R^{19} represents a hydrogen atom, a lower alkyl group, a lower alkoxyalkyl group, an acyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; R^{20}, R^{21} and R^{22}, each of which may be the same or different from one another, represent each a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a lower alkyl group, a lower alkoxy group, a lower alkoxyalkyl group, a lower alkenyl group, an acyl group, an acylamino group, an alkylsulfonylamino group, a hydroxyiminoalkyl group, an alkyloxycarbonylamino group, an alkyloxycarbonyloxy group or a heteroaryl group which may be substituted; or, further, two of R^{20}, R^{21} and R^{22} may together form a saturated or unsaturated ring which may contain a nitrogen atom, a sulfur atom or an oxygen atom; and r represents 0 or an integer of 1 to 8)].

WO 93/06104 discloses compounds of the formula



(I)

or a pharmaceutically acceptable salt thereof,

wherein R^1 is methyl or ethyl;

R^2 is ethyl or n-propyl;

and R^3 and R^4 are each indepdendently H, or C_1-C_6 alkyl optionally substituted with C_5-C_7 cycloalkyl or with morpholino.

Preferred compounds include:

5-[2-ethoxy-5-(3-morpholinopropylsulphamoyl)-phenyl]-1,3-dimethyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

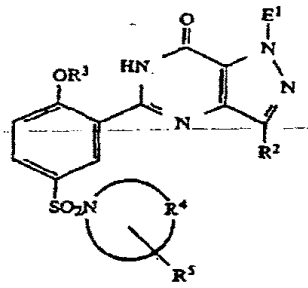
1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxy-phenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

and 5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and pharmaceutically acceptable salts thereof.

U.S. Patent No. 5,346,901 discloses compounds of the formula



(I)

wherein

R^1 is H, C_1–C_3 alkyl, C_3–C_5 cycloalkyl or C_1–C_3 perfluoroalkyl;

R^2 is H, C_1–C_6 alkyl optionally substituted by OH, C_1–C_3 alkoxy or C_3–C_6 cycloalkyl, or C_1–C_3 perfluoroalkyl;

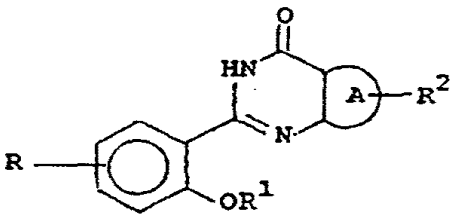
R^3 is C_1–C_6 alkyl, C_3–C_6 alkenyl, C_3–C_6 alkynyl, C_3–C_7 cycloalkyl, C_1–C_6 perfluoroalkyl or (C_3–C_6 cycloalkyl)C_1–C_6 alkyl;

R^4 taken together with the nitrogen atom to which it is attached completes a pyrrolidinyl, piperidino, or morpholino group;

R^5 is H, C_1–C_4 alkyl, C_1–C_3 alkoxy, NR^7R^8, or $CONR^7R^8$;

R^7 and R^8 are each independently H, C_1–C_4 alkyl, (C_1–C_3 alkoxy)C_2–C_4 alkyl or hydroxy C_2–C_4 alkyl; and pharmaceutically acceptable salts thereof.

European published patent application No. 0442204 discloses compounds of the formula



(1)

or a pharmaceutically acceptable salt thereof, wherein

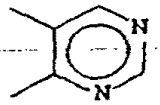
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkyl C_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups ;

R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, -NHCOR^3 wherein R^3 is hydrogen or C_{1-6} alkyl, or -NR^4R^5, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-6}cycloalkyl or C_{1-6}alkyl which is optionally substituted by -CF_3, phenyl, -$S(O)_nC_{1-6}$ alkyl wherein

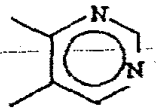
n is 0, 1 or 2, -OR^6, -CO_2R^7 or -NR^8R^9 wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -$S(O)_nC_{1-6}$alkyl, -OR^6 or -NR^8R^9 groups ;

R is halo, C_{1-4}alkyl, C_{1-4}alkoxy, cyano, -$CONR^{10}R^{11}$, CO_2R^{12}, C_{1-4} alkyl$S(O)_n$, -NO_2, -NH_2, -NHCOR^{13} or $SO_2NR^{14}R^{15}$ wherein n is 0, 1 or 2 and R^{10} to R^{15} are independently hydrogen or C_{1-4} alkyl ; and

is a ring of sub-formula (a) or (b) :



(a)

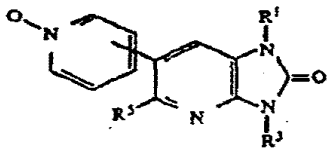


(b).

Preferred compounds include:

2-(5-cyano-2-propoxyphenyl)-7-methylthiopyrimido-[4,5-d]]pyrimidin-4(3H)-one,
2-(5-carboxamido-2-propoxyphenyl)-7-methylthiopyrimido[4,5-d]pyrimido-4(3H)-one, or
2-(5-carboxamido-2-propoxyphenyl)-7-cyclopropylamino[4,5-d]pyrimido-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

U.S. Patent No. 5,010,086 discloses compounds of the formula

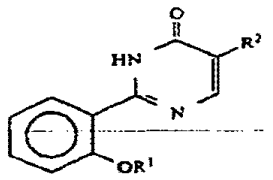


wherein
R_1 and R_3 are hydrogen or lower-alkyl;
R_5 is lower-alkyl or fluorinated lower-alkyl; and the pyridine-N-oxide is attached at the 4- or 3-position; or a pharmaceutically acceptable acid-addition salt thereof.

Preferred compounds include:

1,3-Dihydro-6-(4-pyridinyl)-5-trifluoromethyl-2H-imidazo[4,5-b]pyridin-2-one N-(py)-oxide

U.S. Patent No. 5,290,933 discloses compounds of the formula



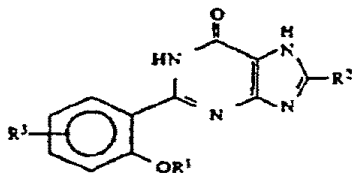
(I)

or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, phenylC_{1-6}alkyl or C_{1-6}alkyl substituted by 1 to 6 fluoro groups; and R^2 is hydrogen, —NHCOR^3, or —CONR^{4}R^5, wherein R^3 is C_{1-6}alkyl, R^4 is C_{1-6}alkyl and R^5 is hydrogen or C_{1-6}alkyl.

Preferred compounds include:

N-methyl 1,6-dihydro-6-oxo-2-(2-propoxypnenyl)-pyrimidine-5-carboxamide,
N,N-dimethyl 1,6-dihydro-6-oxo-2-(2-propoxyphenyl)-pyrimidine-5-carboxamide,
5-acetamido-2-(2-propoxyphenyl)pyrimidin-4(3H)-one, or
2-(2-propoxyphenyl)pyrimidin-4(3H)-one,
or a pharmaceutically acceptable salt thereof.

U.S. Patent No. 5,073,559 discloses compounds of the formula



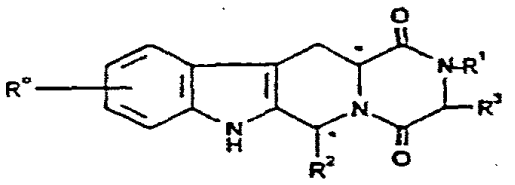
(I)

or pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-4}alkyl, phenylC_{1-4}alkyl or C_{1-4}alkyl substituted by 1 to 6 fluoro groups;
R^2 is hydrogen, hydroxy, C_{1-4}alkyl, phenyl, mercapto, C_{1-4}alkylthio, CF_3 or amino
R^3 is hydrogen, nitro, amino, C_{1-4}alkanoylamino, C_{1-4}-alkoxy, C_{1-4}alkyl, halo, $SO_2NR^4R^5$, $CONR^4R^5$, cyano or C_{1-4}alkyl$S(O)_n$;
R^4 and R^5 are independently hydrogen or C_{1-4}alkyl; and
n is 0, 1 or 2;
provided that R^3 is not hydrogen when R^1 is C_{1-6}alkyl or C_{2-6}alkenyl and R^2 is hydrogen or hydroxy.

Preferred compounds include:

2-(2 2-[2,2,2-trifluoroethoxy]phenyl)purin-6-one,
2-(2 2-cyclopropylmethoxyphenyl)purin-6-one,
2-(2 2-benzyloxyphenyl)purin-6,8-dione,
2-(2 2-propoxyphenyl)-8-trifluoromethylpurin-6-one,
2-(2 2-propoxyphenyl)-8-phenylpurin-6-one,
2-(2 2-propoxyphenyl)-8-methylpurin-6-one,
2-(2-propoxyphenyl)-8-mercaptopurin-6-one,
2-(2 2-propoxyphenyl)-8-methylthiopurin-6-one,
2-(2 2-propoxyphenyl)-8-aminopurin-6-one,
2-(2 2-propoxy-5-nitrophenyl)purin-6-one,
2-(2 2-propoxy-5-aminophenyl)purin-6-one,
2-(2-(2-propoxy-5-acetamidophenyl)purin-6-one,
2-(2 2-propoxy-4-methoxyphenyl)purin-6-one,
2-(2 2-propoxy-5-methoxyphenyl)purin-6-one,
2-(2 2-propoxy-4-methylphenyl)purin-6-one,
2-(2 2-propoxy-5-fluorophenyl)purin-6-one,
2-(2 2-propoxy-5-dimethylsulphamoylphenyl)purin-6-one,
2-(2 2-propoxy-5-methylsulphamoylphenyl)purin-6-one,
2-(2 2-propoxy-5-sulphamoylphenyl)purin-6-one,
2-(2 2-propoxy-4-methylthiophenyl)purin-6-one,
2-(2 2-propoxy-5-cyanophenyl)purin-6-one, and
2-(2-(2-propoxy-5-carbamoylphenyl)purin-6-one,
or a pharmaceutically acceptable salt thereof.

International Patent Publication PCT/EP96/03024 (WO97/03675) discloses compounds of the formula:

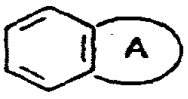


(I)

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

R^o represents hydrogen, halogen or C_{1-6} alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

R^2 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

R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

Preferred compounds include:

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)-pyrrolo[1",2" : 4',5']pyrazino[2',1' : 6,1]pyrido[3,4-b]indole-5-1,4-dione;
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;
(3S, 6R,12aR)-2,3,6,7,12,12a-hexahydro-3-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.

The specific compounds of the invention are:

(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 (Compound A); and

(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 (Compound B);

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

Examples of cGMP PDE inhibitors contemplated in this invention are also described in United States Patent No. 5,346,901 and published International Patent Publication WO 94/28902, both of which documents are incorporated herein by reference.

Sildenafil, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-piperazine, and salts thereof are disclosed in WO 94/28902.

Phentolamine, 3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl)amino]phenol, and salts and esters thereof, and the use of phentolamine in the treatment of sexual dysfunction is disclosed in United States Patent No. 5,731,339, also incorporated herein by reference.

Sildenafil and phentolamine are each known to treat sexual dysfunction. The effectiveness of phentolamine for treatment of sexual dysfunction is demonstrated by test procedures described in U.S 5,731,339. Similar procedures can be used to determine the effectiveness of sildenafil and combinations of phentolamine and sildenafil.

Since the present invention relates to a method of treatment comprising the administration of a combination of two components, the components can be co-administered simultaneously or sequentially. Alternatively, a single pharmaceutical composition comprising sildenafil, or a pharmaceutically acceptable salt thereof, and phentolamine, or a

pharmaceutically acceptable salt or ester thereof, in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral dosage form such as a capsule, tablet, chewable tablets, powder, cachet, suspension or solution. The formulations can be prepared using conventional pharmaceutical excipients and additives using conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

Information on formulations comprising sildenafil are disclosed in WO 94/28902. Representative formulations comprising phentolamine are disclosed in U.S. 5,731,339. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms as disclosed in the aforementioned patent or application may readily be modified using the knowledge of one skilled in the art.

A typical formulation for sildenafil comprises 25, 50 or 100 mg of active and as inactive ingredients, microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hydroxypropylmethylcellulose, titanium dioxide, lactose, triacetin, and FD&C Blue #2 aluminum lake.

A typical formulation for phentolamine is as follows:

Component	mg/Tablet (w/w%)
phentolamine mesylate, USP	40 (10)
Microcrystalline Cellulose, NF	341.6 (85.4)
Croscarmellose Sodium, NF	16 (4.0)
Colloidal Silicon Dioxide, NF	0.4 (0.1)
Magnesium Stearate, NF	2 (0.5)
Total	400 (100)

The following are exemplary formulations for the phentolamine mesylate/sildenafil citrate combination:

Direct Compression Formulation

Component	mg/Tablet
Phentolamine Mesylate	80
Sildenafil Citrate	100
Microcrystalline Cellulose	207.5-209.0
Croscarmellose Sodium	10
Silicon Dioxide	0.5
Magnesium Stearate	0.5-2
Total	400

The direct -compression formulation is manufactured by blending the active ingredients and excipients and compressing the mixture into tablets.

Wet-Granulation Formulation

Component	mg/Tablet
Phentolamine Mesylate	80
Sildenafil Citrate	100
Microcrystalline Cellulose	80
Lactose	114-115.5
Sodium Starch Glycolate	12
Povidone	12
Water	(evaporates)
Magnesium Stearate	0.5-2
Total	400

The wet-granulation formulation is manufactured using the following steps:

1. the active ingredients are combined with microcrystalline cellulose, lactose and sodium starch glycolate in a mixer/granulator;
2. povidone is added to water to form a solution;
3. the granulating solution (from step 2) is added to the powder blend (from step 1) with agitation to form a granulation, and the resulting granulation is dried;
4. the dry granulation is blended with magnesium stearate; and

5. the mixture is compressed into tablets.

Fast-Dissolving Formulations

A

Component	mg/Tablet
Phentolamine Mesylate	40
Sildenafil Citrate	50
Gelatin	30
Mannitol	29
Flavor	1
Water	(evaporates)
Total Dry Tablet Weight	150

The above tablet form is manufactured by:

1. forming a uniform dispersion achieved by adding the active ingredients and excipients to water with agitation;
2. filling aliquots of the dispersion into molds; and
3. lyophilizing to form dry tablets.

B

Component	mg/Tablet
Phentolamine Mesylate	40
Sildenafil Citrate	50
Microcrystalline Cellulose	95
Crospovidone	10
Sodium Bicarbonate	2
Citric Acid	2
Flavor	1
Total	200

The tablets are made by blending the combination of the actives and excipients and compressing the mixture into tablets.

The compounds in the combination of this invention for tr ating sexual dysfunction are administered in accordance with the treatment regimens described in each of the above listed publications. For example, for a combination of a Type V cGMP PDE inhibitors such as

Sildenafil in combination with phentolamine, the typical dosage is 5 to 100 mg of Sildenafil and 5 to 75 mg of phentolamine per dose, usually administered approximately one hour prior to intercourse. It is expected that the dosage of the individual components in the combination will be less than the dosage required when the individual components are administered alone. The exact dose of either component of the combination to be administered and the timing thereof is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient. Where the components of a combination are administered separately, the separate dosage forms need not be administered simultaneously.

Since the present invention relates to treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: for example, a sildenafil pharmaceutical composition and a phentolamine pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. tablet and capsule) or are administered at different dosage intervals.

What is claimed is:

1. A pharmaceutical composition for the treatment of human sexual dysfunction comprising a therapeutically effective amount of phentolamine or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a cGMP PDE V inhibitor or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

2. A composition of claim 1 wherein the cGMP PDE V inhibitor is sildenafil or a pharmaceutically acceptable salt or solvate thereof.

3. The composition of claim 1 wherein the phentolamine is phentolamine mesylate.

4. The composition of claim 1 wherein the sildenafil is sildenafil citrate.

5. The composition of claim 1 wherein the phentolamine is phentolamine mesylate and the cGMP PDE V inhibitor is sildenafil citrate.

6. A method of treating human sexual dysfunction comprising the simultaneous or sequential administration of a therapeutically effective amount of phentolamine or a pharmaceutically acceptable salt, solvate or ester thereof, and a therapeutically effective amount of a cGMP PDE V inhibitor or a pharmaceutically acceptable salt thereof.

7. The method of claim 6 wherein the cGMP PDE V inhibitor is sildenafil or a pharmaceutically acceptable salt or solvate thereof.

8. The method of claim 6 wherein the phentolamine is phentolamine mesylate.

9. The method of claim 6 wherein the cGMP PDE V inhibitor is sildenafil citrate.

10. The method of claim 6 wherein the phentolamine is phentolamine mesylate and the cGMP PDE inhibitor V is sildenafil citrate.

11. A kit comprising in separate containers in a single package, pharmaceutical compositions for use in combination to treat sexual dysfunction which comprises in one container a therapeutically effective amount phentolamine or a pharmaceutically acceptable salt, solvate or ester thereof in a pharmaceutically acceptable carrier and in a second container a therapeutically effective amount of a cGMP PDE V inhibitor or a pharmaceutically acceptable salt of solvate thereof in a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for the treatment of human sexual dysfunction comprising a therapeutically effective amount of a first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a second vasodilating agent or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12 wherein said first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is an adrenergic blocker.

14. The pharmaceutical composition of claim 13 wherein said adrenergic blocker is an alpha-adrenergic blocker.

15. The pharmaceutical composition of claim 14 wherein alpha adrenergic blocker is selected from the group consisting of an alpha1-adrenergic blocker, an alpha2-adrenergic blocker or both an alpha1-adrenergic blocker and an alpha2-adrenergic blocker.

16. The pharmaceutical composition of claim 12 wherein said second vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is a cGMP PDE inhibitor.

17. The pharmaceutical composition of claim 12 wherein said first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof is an adrenergic blocker and said second vasodilating agent

or a pharmaceutically acceptable salt or solvate or ester thereof is a cGMP PDE inhibitor.

18. The pharmaceutical composition of claim 17 wherein the adrenergic blocker is selected from the group consisting of phentolamine, phentolamine mesylate, phentolamine hydrochloride, phenoxybenazmine, tolazoline, dibenamine, yohimbine, terazosin, doxazosin and prazosin.

19. The pharmaceutical composition of claim 17 wherein the cGMP PDE inhibitor is a cGMP PDE V inhibitor.

20. The pharmaceutical composition of claim 17 wherein the cGMP PDE V inhibitor is selected from the group consisting of: sildenafil,
(6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrizino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound A), and
(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 (Compound B) or a pharmaceutically acceptable salt or solvate thereof.

21. A method of treating human sexual dysfunction comprising the simultaneous or sequential administration of a therapeutically effective amount of a therapeutically effective amount of a first vasodilating agent or a pharmaceutically acceptable salt or solvate or ester thereof, a therapeutically effective amount of a second vasodilating agent or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07046

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GOMAA A ET AL: "Topical treatment of erectile dysfunction: randomised double blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate 'see comments!." BMJ (CLINICAL RESEARCH ED.), (1996 JUN 15) 312 (7045) 1512-5. , XP002115285 abstract the whole document ---	12-15,21
P,X	SOLI M ET AL: "Vasoactive cocktails for erectile dysfunction: chemical stability of PGE1, papaverine and phentolamine." JOURNAL OF UROLOGY, (1998 AUG) 160 (2) 551-5. , XP002115286 abstract the whole document ---	12-15,21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 1999	28/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Economou, D

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PC1/US 99/07046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHAO R ET AL: "Experience with intracavernosal tri-mixture for the management of neurogenic erectile dysfunction." ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION, (1994 MAR) 75 (3) 276-8 , XP002115287 abstract page 277, left-hand column, paragraph 4 - right-hand column, paragraph 3 ---	12-15,21
X	MIRONE V ET AL: "Ketanserin plus prostaglandin E1 (PGE-1) as intracavernosal therapy for patients with erectile dysfunction unresponsive to PGE-1 alone." BRITISH JOURNAL OF UROLOGY, (1996 MAY) 77 (5) 736-9. , XP002115288 abstract page 737, right-hand column, paragraph 4 - page 738, left-hand column, paragraph 3 page 736, left-hand column, line 1 - right-hand column, paragraph 2 ---	12-15,21
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/07046

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/031,556	William Ernest Pullman	29342/36206A

INTERNATIONAL APPLICATION NO.	
PCT/US00/11129	
I.A. FILING DATE	PRIORITY DATE
04/26/2000	04/30/1999

04743
MARSHALL, GERSTEIN & BORUN
6300 SEARS TOWER
233 SOUTH WACKER
CHICAGO, IL 60606-6357

CONFIRMATION NO. 6526

371 ACCEPTANCE LETTER

OC000000007731069

Date Mailed: 04/02/2002

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.494 OR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as an Elected Office (37 CFR 1.495) , has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

10/19/2001	10/19/2001
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF RECEIPT OF ALL 35 U.S.C. REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- U.S. Basic National Fee
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Oath or Declaration
- Preliminary Amendments

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

SHAKEEL AHMED
Telephone: (703) 305-3659

PART 3 - OFFICE COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 139755-83-2 REGISTRY
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrazolo[4,3-d]pyrimidine, piperazine deriv.
OTHER NAMES:
CN 5-[2-Ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one
CN **Sildenafil** VIAGRA
FS 3D CONCORD
MF C22 H30 N6 O4 S
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
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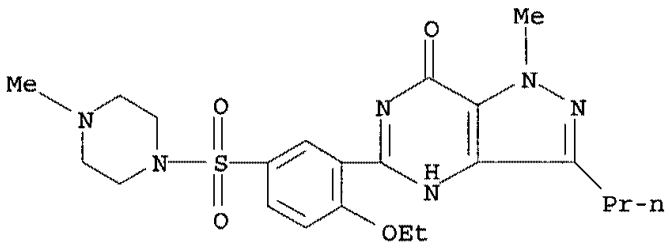

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

389 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
393 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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STRUCTURE FILE UPDATES:   15 JUL 2002  HIGHEST RN 438572-95-3
DICTIONARY FILE UPDATES:  15 JUL 2002  HIGHEST RN 438572-95-3

TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

  Please note that search-term pricing does apply when
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Calculated physical property data is now available.  See HELP PROPERTIES
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Registry File, for complete details:
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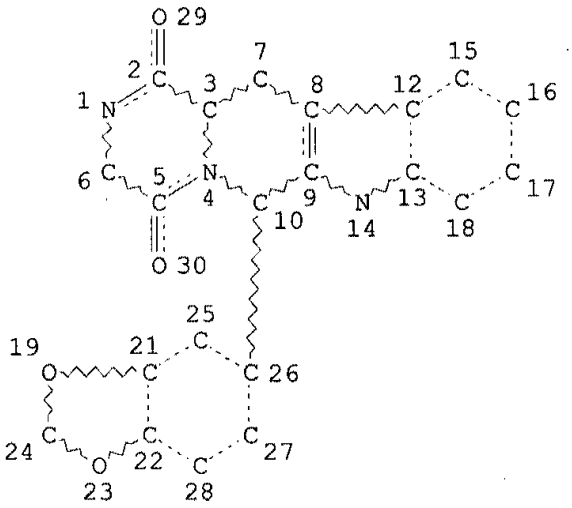


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NODE ATTRIBUTES:
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GRAPH ATTRIBUTES:
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STEREO ATTRIBUTES: NONE
L10          178 SEA FILE=REGISTRY SSS FUL L8

100.0% PROCESSED    189 ITERATIONS                    178 ANSWERS
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FILE COVERS 1907 - 16 Jul 2002 VOL 137 ISS 3
FILE LAST UPDATED: 15 Jul 2002 (20020715/ED)

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L10         178 SEA FILE=REGISTRY SSS FUL L8
L11          38 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10
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L10         178 SEA FILE=REGISTRY SSS FUL L8
L11          38 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10
L12          37 SEA FILE=CAPLUS ABB=ON  PLU=ON  L11 AND PHARMAC?/SC,SX
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=> d ibib abs hitstr l12 1-37

L12  ANSWER 1 OF 37  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:427673  CAPLUS
DOCUMENT NUMBER:          137:3711
TITLE:                    Cells and animals homozygous or heterozygous for a
                          knockout of the PDE11A gene and their uses
INVENTOR(S):              Burslem, Martin F.; Harrow, Ian Dennis; Lanfear,
                          Jeremy; Phillips, Stephen C.
PATENT ASSIGNEE(S):       Pfizer Limited, UK; Pfizer Inc.
SOURCE:                   Eur. Pat. Appl., 31 pp.
                          CODEN: EPXXDW
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     EP 1211313         A2   20020605      EP 2001-308959   20011022
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
```

PRIORITY APPLN. INFO.: GB 2000-26727 A 20001101
GB 2001-11710 A 20010514

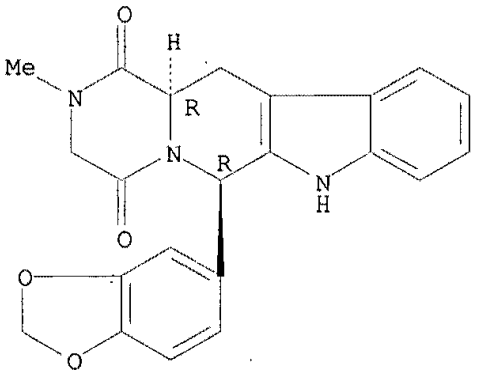
AB Animal cells and animals carrying a knockout of the gene for the cyclic nucleotide phosphodiesterase PDE11 are described for use in anal. of the role of the enzyme, esp. in spermatogenesis and in the screening of drugs for regulation of spermatogenesis. Heterozygous knockout mice show lowered levels of spermatogenesis. The effect of the knockout on patterns of gene expression was analyzed by microarray hybridization. Known inhibitors of cyclic nucleotide phosphodiesterases were tested for their ability to inhibit PDE11. The pattern of inhibition was similar to, but distinct from, that for PDE5. Array hybridization was used to analyze the effects of PDE11 knockout on gene expression in testis. Twenty-four genes (18 down-regulated and 6 up-regulated) were identified. These gene products may themselves be therapeutic targets for PDE11-related disease (no data).

IT **171596-29-5**, IC-351
RL: PAC (Pharmacological activity); BIOL (Biological study)
(as inhibitor of PDE11; cells and animals homozygous or heterozygous for knockout of PDE11A gene and their uses)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L12 ANSWER 2 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:391540 CAPLUS
DOCUMENT NUMBER: 136:380144
TITLE: Phosphodiesterase V inhibitors for the treatment of premature ejaculation
INVENTOR(S): Boolell, Mitradev
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002040027	A1	20020523	WO 2001-IB2180	20011119

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002091129 A1 20020711 US 2001-990955 20011116
PRIORITY APPLN. INFO.: GB 2000-28245 A 20001120
US 2001-260564P P 20010109

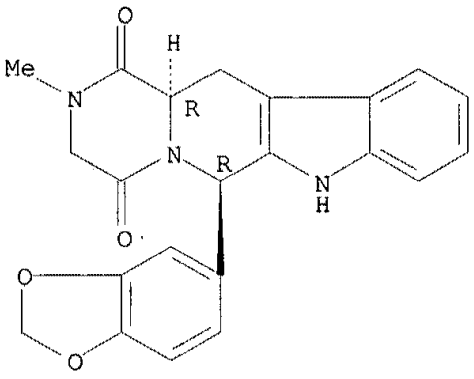
AB The invention relates to the use of cGMP phosphodiesterase V inhibitors, including in particular the compd. sildenafil, for the treatment of premature ejaculation in patients with normal erectile function.

IT **171596-29-5**, IC 351
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase V inhibitors for treatment of premature ejaculation)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:353456 CAPLUS
DOCUMENT NUMBER: 136:369739
TITLE: Preparation of pyrazino[1',2':1,6]pyrido[3,4-b]indole derivatives as phosphoesterase inhibitors for use as therapeutic agents
INVENTOR(S): Orme, Mark W.; Sawyer, Jason Scott; Schultze, Lisa M.
PATENT ASSIGNEE(S): Lilly Icos L.L.C., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

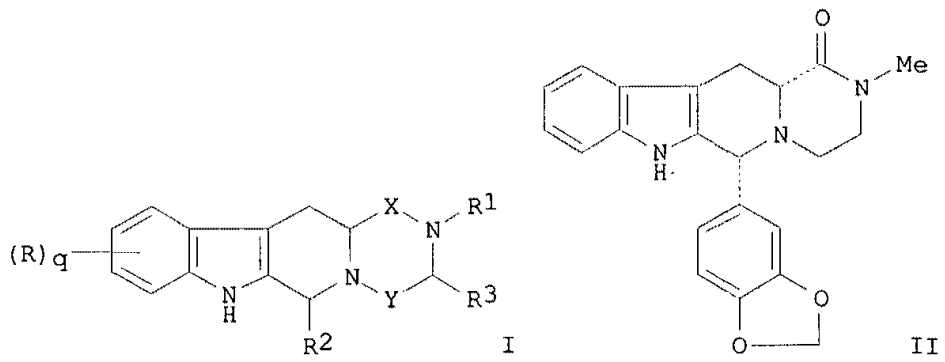
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036593	A1	20020510	WO 2001-US31364	20011009

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-246257P P 20001106
OTHER SOURCE(S): MARPAT 136:369739

GI



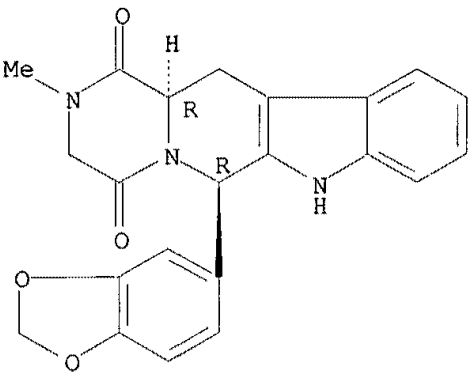
AB 2,3,6,7,12,12A-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole derivs., such as I [R = halo, alkyl; R1 = H, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heteroarylalkyl, etc.; R2 = monocyclic arom. ring, such as benzene, thiophene, furan, pyridine, etc.; R3 = H, alkyl; R1,R3 = fused carbocyclic ring; X, Y = CO, SO, SO2, CS, C(Ra)2; Ra = H, alkyl, benzyl; q = 0-4], pharmaceutically acceptable salts and solvates thereof, were prepd. for pharmaceutical use as phosphodiesterase inhibitors for the treatment of conditions, such as erectile dysfunction, female arousal disorder, angina, hypertension, and vascular disease. Thus, pyrazinopyridoindole deriv. II was prepd. by a multistep procedure starting with D-Tryptophan Me ester, piperonal and chloroacetaldehyde. The prepd. heterocycles were tested for phosphodiesterase V (PDE5) inhibitory activity with II exhibiting an IC50 of 54 nM.

IT **171596-29-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrazino[1',2':1,6]pyrido[3,4-b]indole derivs. as phosphoesterase inhibitors for use as therapeutic agents)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:241329 CAPLUS
DOCUMENT NUMBER: 136:284433
TITLE: Administration of phosphodiesterase inhibitors for the treatment of premature ejaculation
INVENTOR(S): Wilson, Leland F.; Doherty, Paul C.; Place, Virgil A.; Smith, William L.; Abdel-Hamid, Abdou Ali Ibrahim Aboubakr
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 467,094.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002037828	A1	20020328	US 2001-888250	20010621
US 6403597	B2	20020611		
US 6037346	A	20000314	US 1998-181070	19981027

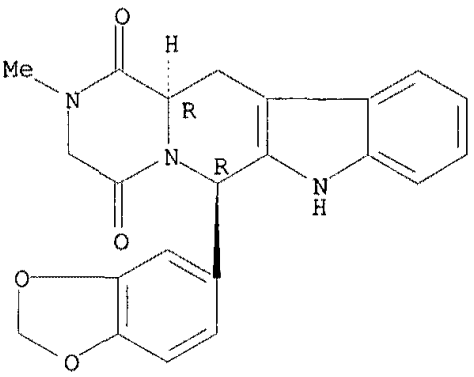
PRIORITY APPLN. INFO.: US 1997-958816 B2 19971028
US 1998-181070 A2 19981027
US 1999-467094 A2 19991210

AB A method is provided for treatment of premature ejaculation by administration of a phosphodiesterase inhibitor, e.g., an inhibitor of a Type III, Type IV, or Type V phosphodiesterase. In a preferred embodiment, administration is on as "as needed" basis, i.e., the drug is administered immediately or several hours prior to sexual activity. Pharmaceutical formulations and packaged kits are also provided. Zaprinast 1.0, mannitol 1.0, microcryst. cellulose 2.0, and magnesium stearate 10 mg are blended in a suitable mixer and then compressed into sublingual tablets. Each sublingual tablet contains 10 mg zaprinast.

IT **171596-29-5**, GF 196960
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GF 196960; administration of phosphodiesterase inhibitors for treatment of premature ejaculation)

RN 171596-29-5 CAPLUS
CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L12 ANSWER 5 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:142493 CAPLUS
DOCUMENT NUMBER: 136:194255
TITLE: Treatment of the insulin resistance syndrome
INVENTOR(S): Fryburg, David Albert; Gibbs, Earl Michael; Koppiker, Nandan Parmanand
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002013798	A2	20020221	WO 2001-IB1428	20010806
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001076607	A5	20020225	AU 2001-76607	20010806

PRIORITY APPLN. INFO.:			
US 2000-224928P	P	20000811
GB 2000-30649	A	20001215
US 2001-266083P	P	20010202
GB 2001-6465	A	20010315
GB 2001-6468	A	20010315
GB 2001-17134	A	20010713
WO 2001-IB1428	W	20010806

AB Use of a selective cGMP PDE5 inhibitor or a pharmaceutical compn. thereof in the prepn. of a medicament for the curative, palliative or prophylactic treatment of the insulin resistance syndrome wherein the insulin resistance syndrome means the concomitant existence in a subject of two or more of: dyslipidemia; hypertension; type 2 diabetes mellitus, impaired glucose tolerance (IGT) or a family history of diabetes; hyperuricemia and/or gout; a pro-coagulant state; atherosclerosis; or truncal obesity wherein said use can occur alone or in combination with other agents to treat the insulin resistance syndrome or individual aspects of the insulin

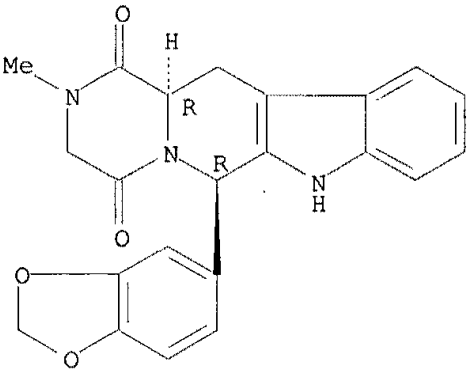
resistance syndrome.

IT **171596-29-5**, IC-351
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of the insulin resistance syndrome)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L12 ANSWER 6 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:122770 CAPLUS
DOCUMENT NUMBER: 136:178015
TITLE: Drugs for incontinence - salified and nonsalified nitric oxide-donors and phosphodiesterase inhibitors
INVENTOR(S): Del Soldato, Piero; Benedini, Francesca
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002011707	A2	20020214	WO 2001-EP8734	20010727
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001091691	A5	20020218	AU 2001-91691	20010727

PRIORITY APPLN. INFO.: IT 2000-MI1848 A 20000808
WO 2001-EP8734 W 20010727

OTHER SOURCE(S): MARPAT 136:178015

AB Use in the incontinence of one or more of the following classes of drugs selected from the following: (B) salified and nonsalified nitric oxide-donor drugs, of formula: A - X1 - N(O)z, (B') nitrate salts of drugs used for the incontinence, and which do not contain in the mol. a nitric oxide donor group; (C) org. or inorg. salts of compds. inhibiting

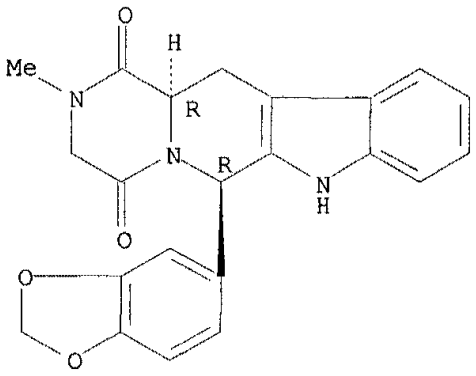
phosphodiesterases.

IT **171596-29-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salified and nonsalified nitric oxide-donors and phosphodiesterase inhibitors for treatment of incontinence)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

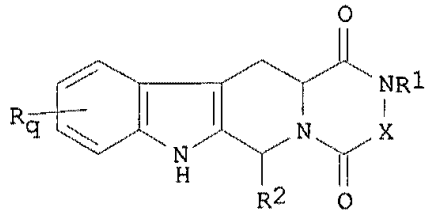


L12 ANSWER 7 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:107344 CAPLUS
DOCUMENT NUMBER: 136:151441
TITLE: Preparation of fused heterocyclic derivatives as phosphodiesterase inhibitors
INVENTOR(S): Orme, Mark W.; Sawyer, Jason Scott; Schultze, Lisa M.
PATENT ASSIGNEE(S): Lilly Icos L.L.C., USA
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002010166	A1	20020207	WO 2001-US21678	20010709

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-222451P P 20000802
OTHER SOURCE(S): MARPAT 136:151441
GI



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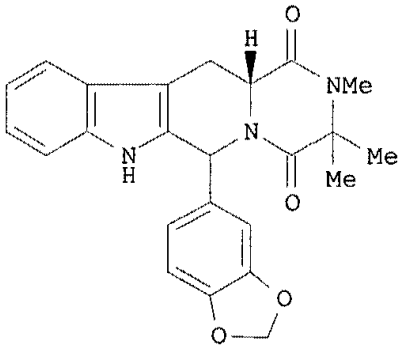


II

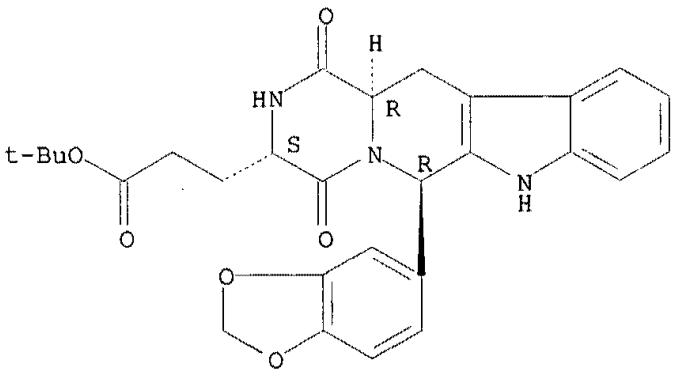
AB Compds. I [R = halo, alkyl; q = 0-4; R1 = H, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl; R2 is an optionally substituted monocyclic arom. ring selected from benzene, thiophene, furan, and pyridine or an optionally substituted bicyclic ring; X = NH or substituted imino, O, S, substituted methylene or ethylene; the substituents may form addnl. rings] and their salts and solvates were prepd. for use as phosphodiesterase (PDE) inhibitors. Thus, compd. II was prepd. by a multistep procedure starting with coupling of L-tryptophan Me ester with CbzNMeCMe2CO2H (Cbz = benzyloxycarbonyl) and showed IC50 = 161.0 nM for inhibition of cGMP-PDE.

IT **395665-39-1P 395665-40-4P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of fused heterocyclic derivs. as phosphodiesterase inhibitors)

RN 395665-39-1 CAPLUS

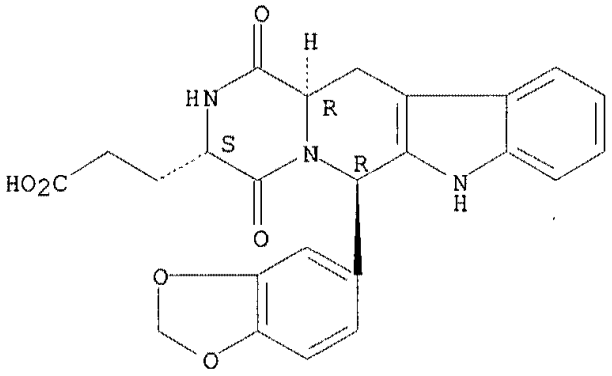
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propanoic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 1,1-dimethylethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 395665-40-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propanoic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

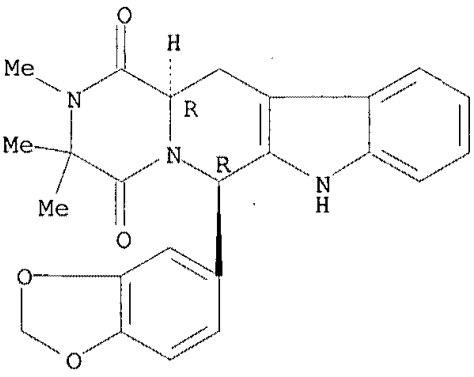
Absolute stereochemistry. Rotation (+).



IT **395665-35-7P 395665-36-8P 395665-41-5P**
395665-42-6P 395665-43-7P 395665-47-1P
395665-49-3P 395665-51-7P 395665-53-9P
395665-55-1P 395665-57-3P 395665-59-5P
395665-61-9P 395665-63-1P 395665-65-3P
395665-67-5P 395665-69-7P 395665-70-0P
395665-71-1P 395665-72-2P 395665-73-3P
395665-75-5P 395665-76-6P 395665-77-7P
395665-78-8P 395665-79-9P 395665-80-2P
395665-81-3P 395665-91-5P 395665-95-9P
395665-96-0P 395665-98-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of fused heterocyclic derivs. as phosphodiesterase inhibitors)

RN 395665-35-7 CAPLUS
CN 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-2,3,3-trimethyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

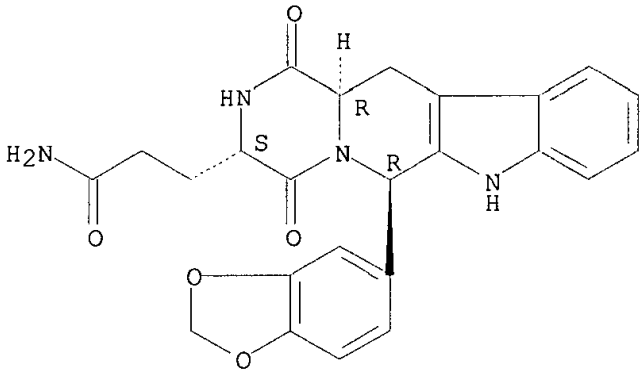
Absolute stereochemistry.



RN 395665-36-8 CAPLUS

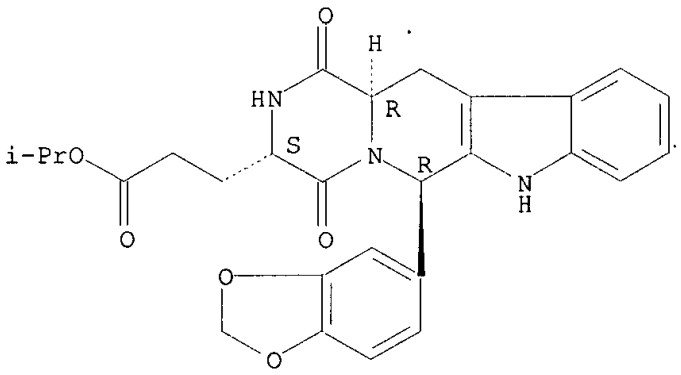
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propanamide, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



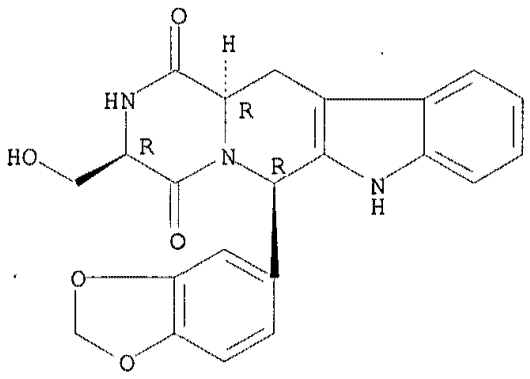
RN 395665-41-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propanoic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 1-methylethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



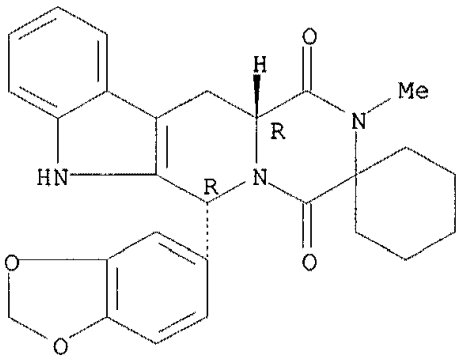
RN 395665-42-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-(hydroxymethyl)-, (3R,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



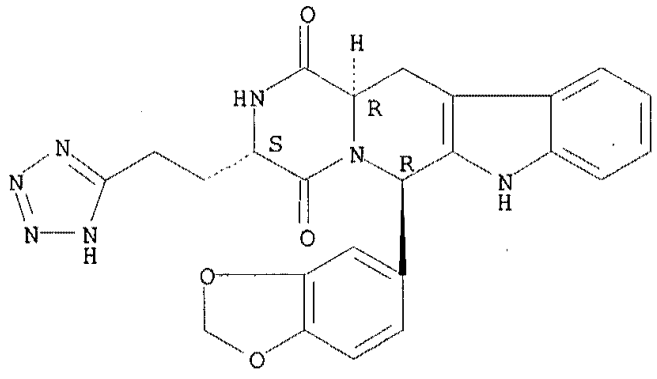
RN 395665-43-7 CAPLUS
CN Spiro[cyclohexane-1,3'(4'H)-pyrazino[1',2':1,6]pyrido[3,4-b]indole]-1',4'(2'H)-dione, 6'-(1,3-benzodioxol-5-yl)-6',7',12',12'a-tetrahydro-2'-methyl-, (6'R,12'aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 395665-47-1 CAPLUS
CN 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-3-[2-(1H-tetrazol-5-yl)ethyl]-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

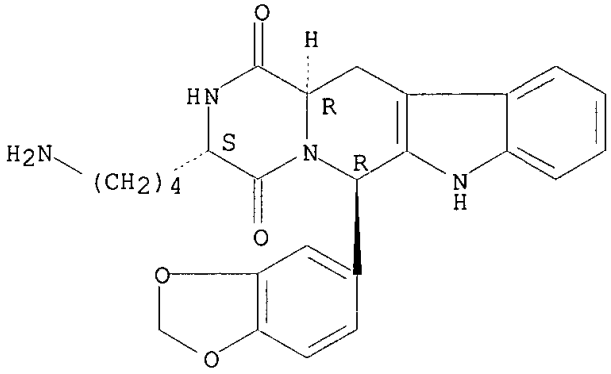
Absolute stereochemistry.



RN 395665-49-3 CAPLUS

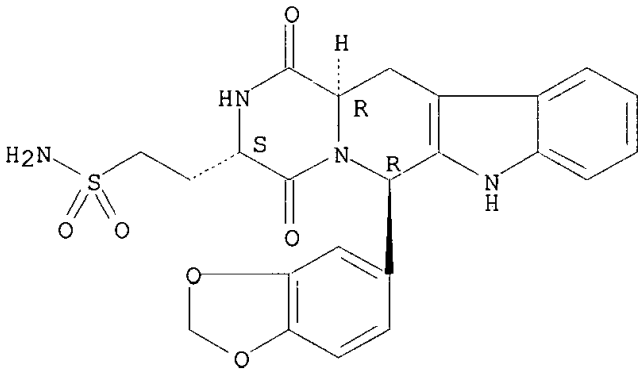
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 3-(4-aminobutyl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



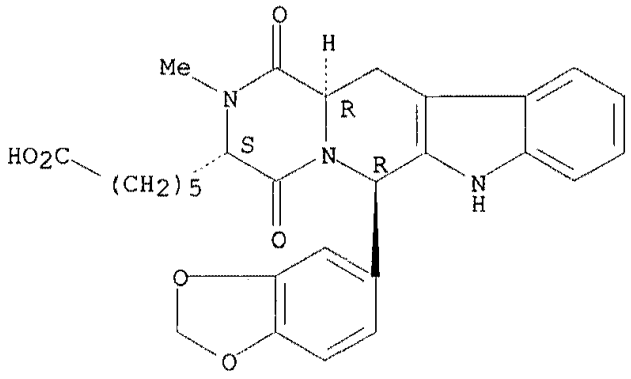
RN 395665-51-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-ethanesulfonamide, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



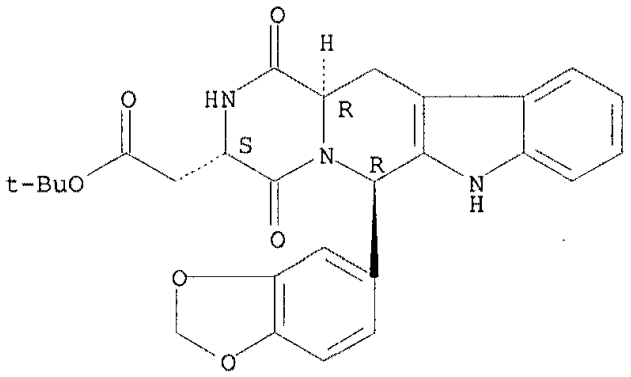
RN 395665-53-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-hexanoic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-2-methyl-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



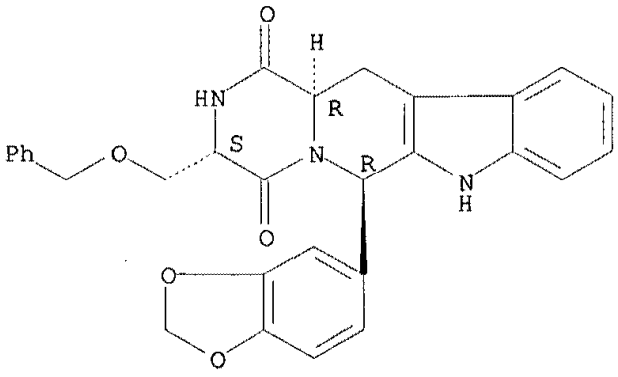
RN 395665-55-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 1,1-dimethylethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 395665-57-3 CAPLUS
CN 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-3-[(phenylmethoxy)methyl]-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

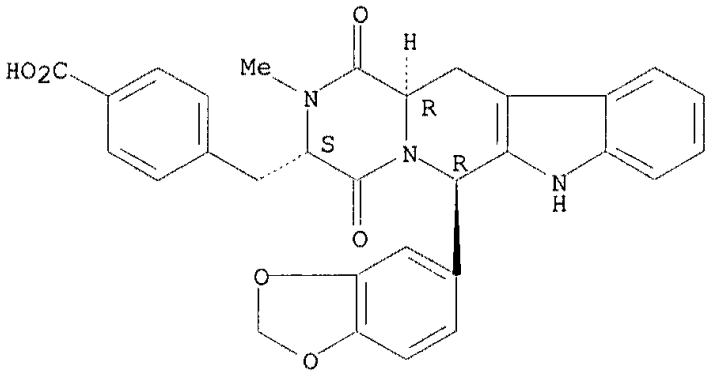
Absolute stereochemistry.



RN 395665-59-5 CAPLUS

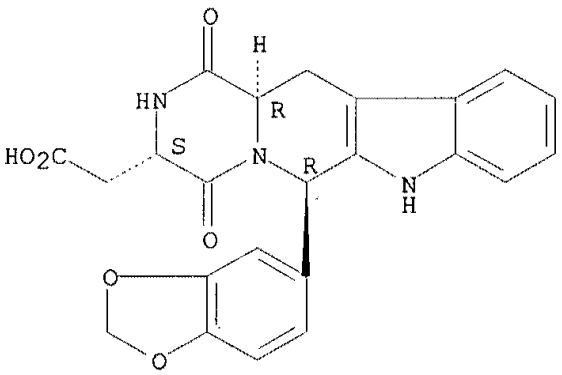
CN Benzoic acid, 4-[[(3S,6R,12aR)-6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-2-methyl-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-3-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



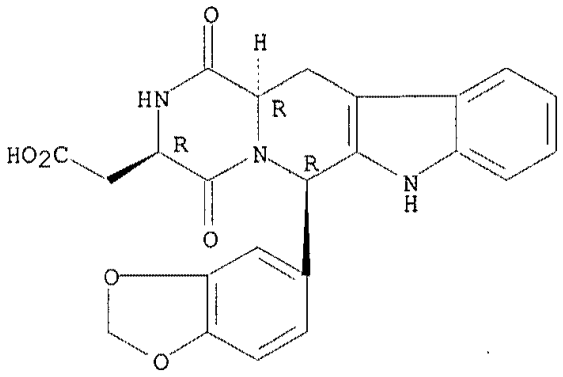
RN 395665-61-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



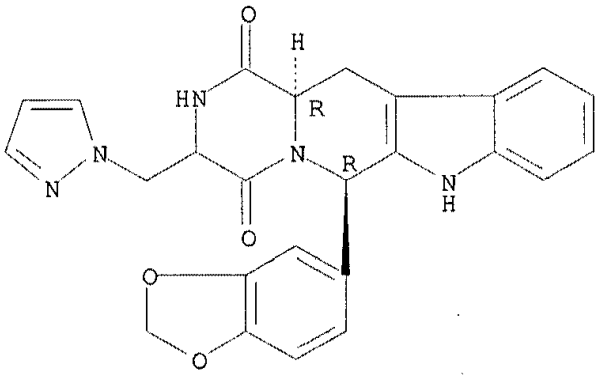
RN 395665-63-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3R,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



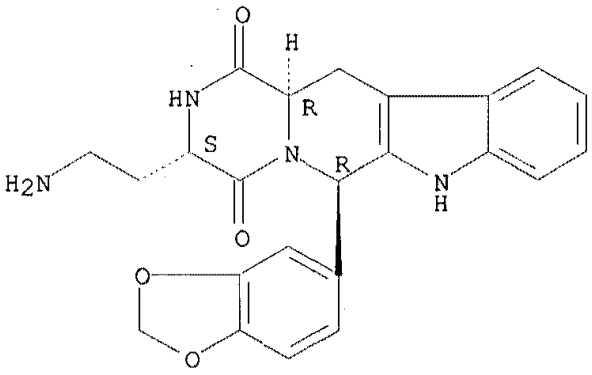
RN 395665-65-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-(1H-pyrazol-1-ylmethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 395665-67-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 3-(2-aminoethyl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

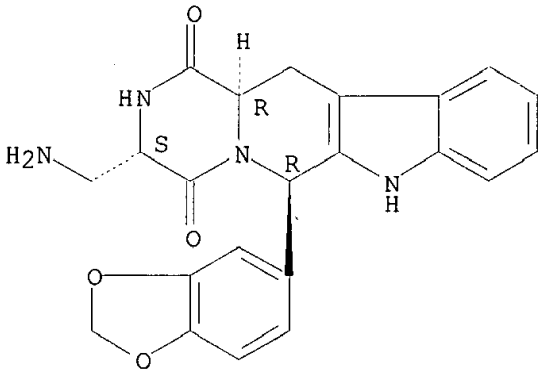
Absolute stereochemistry.



RN 395665-69-7 CAPLUS

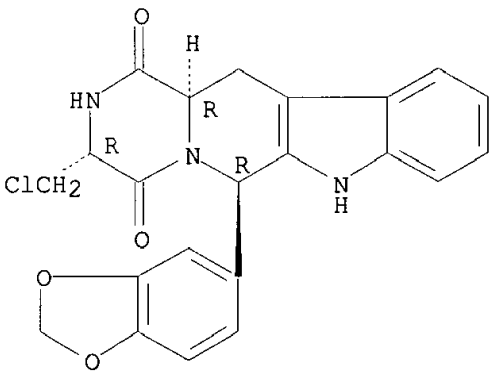
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 3-(aminomethyl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



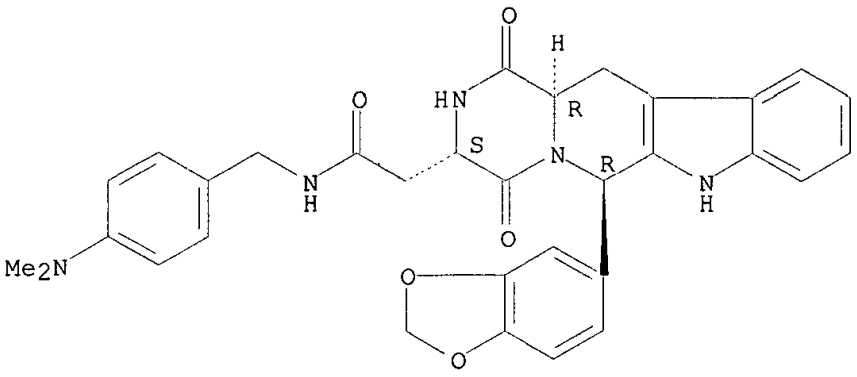
RN 395665-70-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-3-(chloromethyl)-2,3,6,7,12,12a-hexahydro-, (3R,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



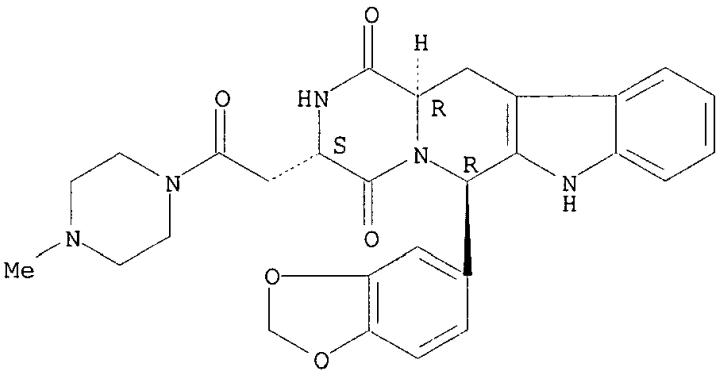
RN 395665-71-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetamide, 6-(1,3-benzodioxol-5-yl)-N-[[4-(dimethylamino)phenyl]methyl]-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



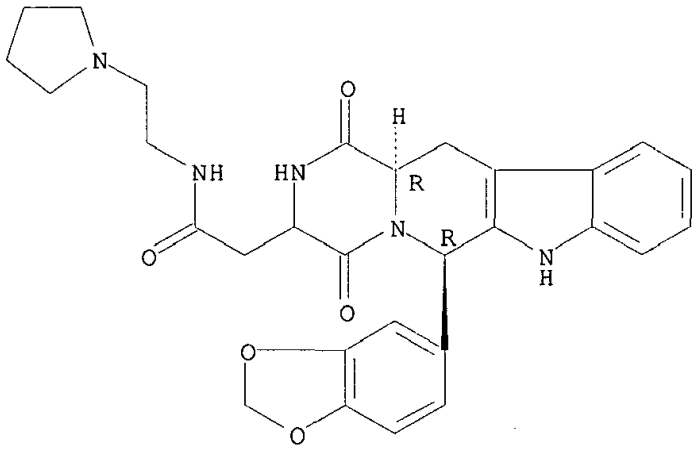
RN 395665-72-2 CAPLUS
CN Piperazine, 1-[[(3S,6R,12aR)-6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-3-yl]acetyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



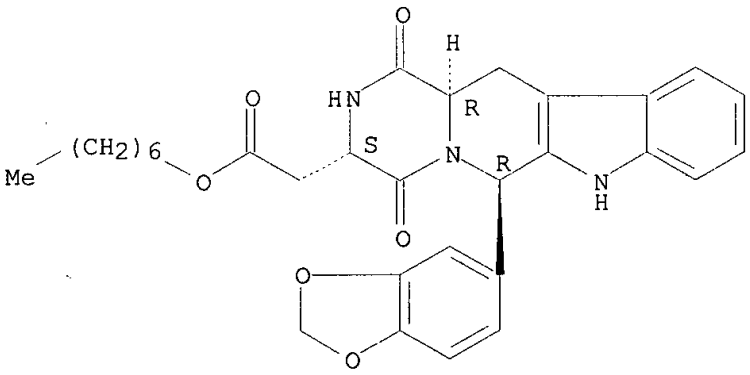
RN 395665-73-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetamide, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-N-[2-(1-pyrrolidinyl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



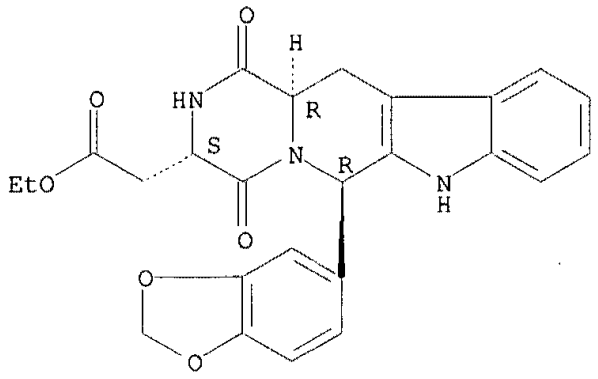
RN 395665-75-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, heptyl ester, (3S,6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



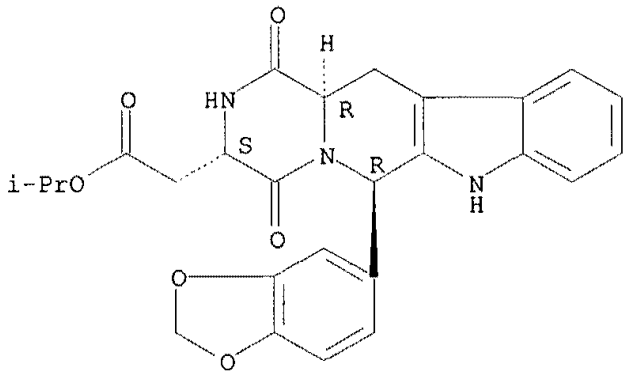
RN 395665-76-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, ethyl ester, (3S,6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



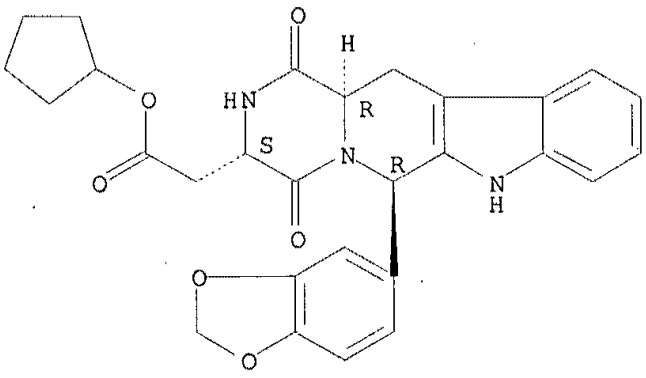
RN 395665-77-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 1-methylethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 395665-78-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, cyclopentyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

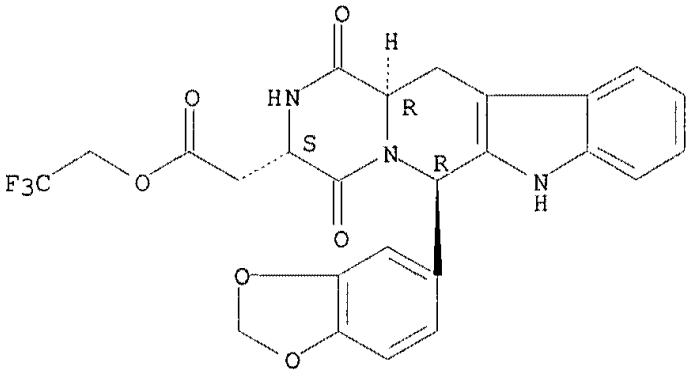
Absolute stereochemistry.



RN 395665-79-9 CAPLUS

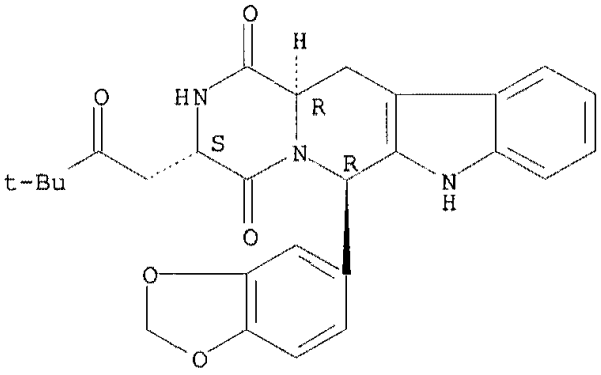
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 2,2,2-trifluoroethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



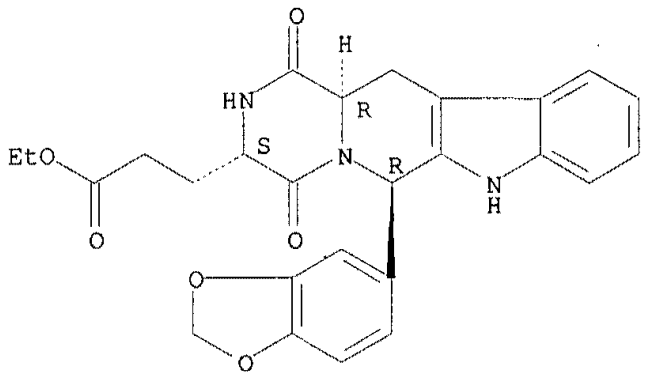
RN 395665-80-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-3-(3,3-dimethyl-2-oxobutyl)-2,3,6,7,12,12a-hexahydro-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



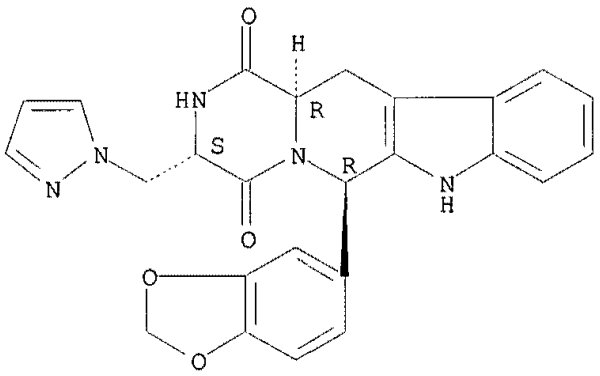
RN 395665-81-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propanoic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, ethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



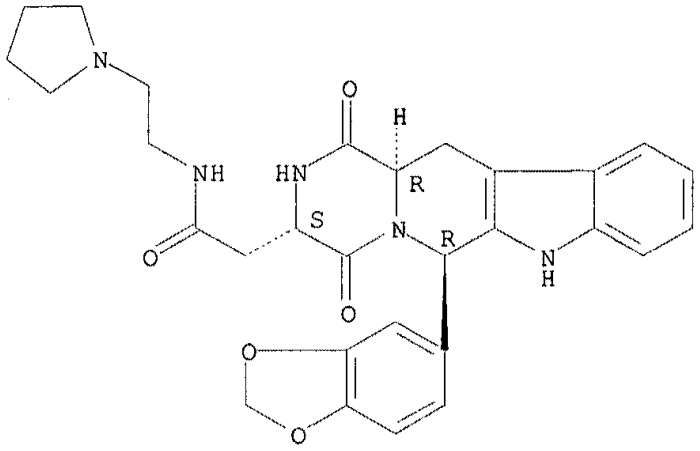
RN 395665-91-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-(1H-pyrazol-1-ylmethyl)-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



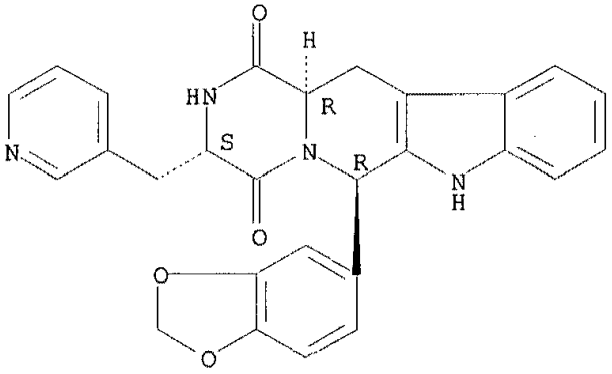
RN 395665-95-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetamide, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-N-[2-(1-pyrrolidinyl)ethyl]-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



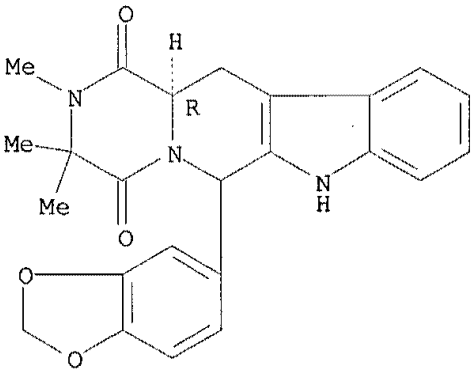
RN 395665-96-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-(3-pyridinylmethyl)-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 395665-98-2 CAPLUS
CN 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-2,3,3-trimethyl-, (12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:51273 CAPLUS
DOCUMENT NUMBER: 136:96099
TITLE: Treatment of male sexual dysfunction
INVENTOR(S): Naylor, Alasdair Mark; Van der Graaf, Pieter Hadewijn; Wayman, Christopher Peter
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002003995	A2	20020117	WO 2001-IB1187	20010702
WO 2002003995	A3	20020418		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002052370	A1	20020502	US 2001-893585	20010628
AU 2001069353	A5	20020121	AU 2001-69353	20010702

PRIORITY APPLN. INFO.:

GB 2000-16684	A	20000706
GB 2000-30647	A	20001215
GB 2001-6167	A	20010313
GB 2001-8483	A	20010404
US 2000-219100P	P	20000718
GB 2001-1584	A	20010122
US 2001-274957P	P	20010312
WO 2001-IB1187	W	20010702

OTHER SOURCE(S): MARPAT 136:96099

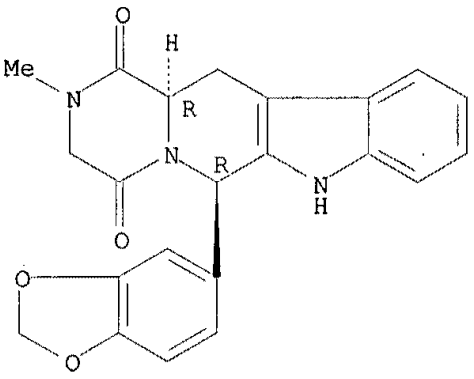
AB The present invention relates to the use of neutral endopeptidase inhibitors (NEPi) and a combination of NEPi and phosphodiesterase type (PDE5) inhibitor for the treatment of male sexual dysfunction, in particular MED.

IT **171596-29-5**, IC-351
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of male sexual dysfunction using neutral endopeptidase inhibitors and their combination with phosphodiesterase type 5 inhibitors and other agents in relation to inhibition of angiotensin converting enzyme)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

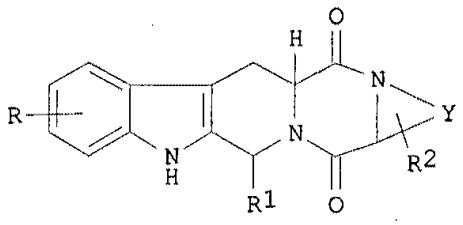


L12 ANSWER 9 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:10477 CAPLUS
DOCUMENT NUMBER: 136:85829
TITLE: preparation of ring fused pyrazinopyridoindole derivatives as cyclic GMP-specific phosphodiesterase inhibitors
INVENTOR(S): Orme, Mark W.; Sawyer, Jason Scott
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000658	A1	20020103	WO 2001-US16164	20010517
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001063278	A5	20020108	AU 2001-63278	20010517

PRIORITY APPLN. INFO.: US 2000-213651P P 20000623
WO 2001-US16164 W 20010517

OTHER SOURCE(S): MARPAT 136:85829
GI



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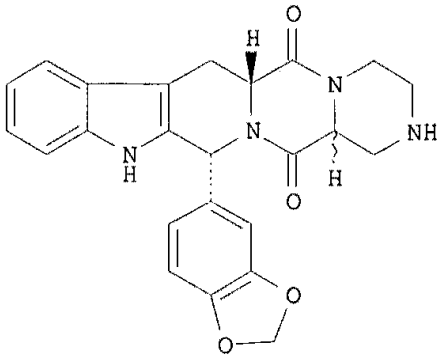


II

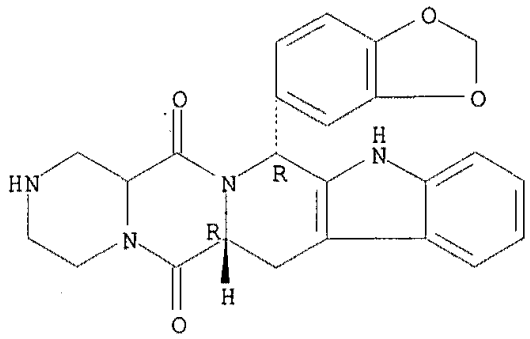
AB The title compds. I (R = halo, C1-6-alkyl; R1 = a nonocyclic arom. ring selected from benzene, thiophene, furan, and pyridine, and an optionally substituted bicyclic ring wherein the fused ring is a 5- or 6-membered ring and optionally with one or two heteroatoms selected from O, S, and N; Y = a 3-, 4-, or 5-membered carbon chain of a 5-, 6-, or 7-membered heteroatom chain of a 5-, 6-, or 7-membered unsubstituted or substituted ring wherein the heteroatom chain contains one or two heteroatoms selected from O, S, N; R2 = nitro, halo, cyano, acyl, acyloxy, C1-4-alkyleneHet, etc.) and their pharmaceutically acceptable salts were prepd. as cyclic GMP-specific phosphodiesterase inhibitors. Thus, N,N'-bis-CBZ-2-carboxypiperazine was treated with Me 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate and the product cyclized by H2 in presence of Pd-C to give the tetraazaindenoanthracenedione II. The IC50 of II as cyclic GMP-specific phosphodiesterase inhibitor was 1.7 nM.

IT **385765-02-6P 385765-03-7P**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of ring fused pyrazinopyridoindole derivs. as cyclic GMP-specific phosphodiesterase inhibitors)

RN 385765-02-6 CAPLUS

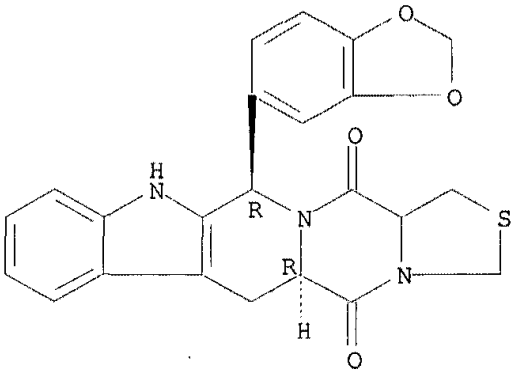
CN 6H-Pyrazino[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-6,15(2H)-dione, 13-(1,3-benzodioxol-5-yl)-1,3,4,6a,7,12,13,15a-octahydro-, (6aR,13R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



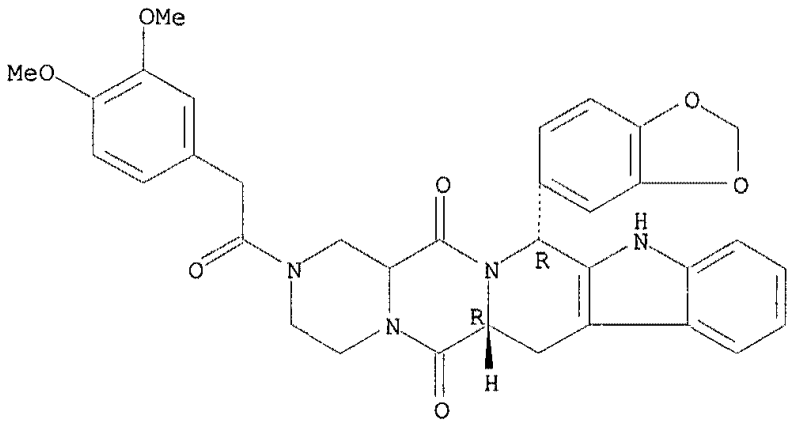
RN 385765-03-7 CAPLUS
CN 3H,5H,14H-Thiazolo[3'',4'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,5a,6,11,12,14a-hexahydro-, (5aR,12R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



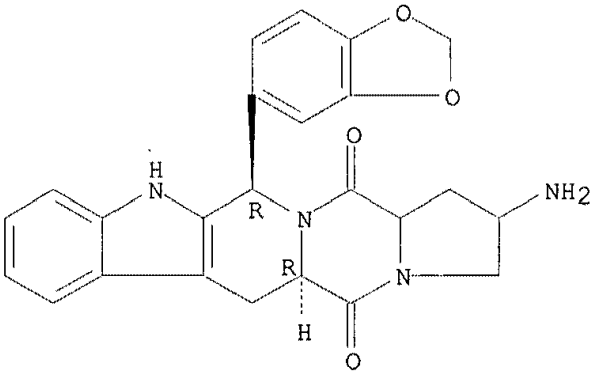
IT **385765-04-8P 385765-05-9P 385765-06-0P**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ring fused pyrazinopyridoindole derivs. as cyclic GMP-specific phosphodiesterase inhibitors)
RN 385765-04-8 CAPLUS
CN 6H-Pyrazino[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-6,15(2H)-dione, 13-(1,3-benzodioxol-5-yl)-2-[(3,4-dimethoxyphenyl)acetyl]-1,3,4,6a,7,12,13,15a-octahydro-, (6aR,13R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



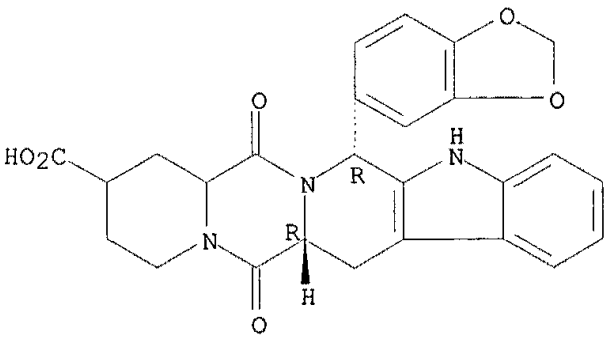
RN 385765-05-9 CAPLUS
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 2-amino-12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 385765-06-0 CAPLUS
CN 5H-Pyrido[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-10-carboxylic acid, 6-(1,3-benzodioxol-5-yl)-6,8,8a,9,10,11,12,14,14a,15-decahydro-8,14-dioxo-, (6R,14aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:10475 CAPLUS
DOCUMENT NUMBER: 136:85828
TITLE: Preparation of pyrazinopyridoindolediones as cyclic GMP phosphodiesterase inhibitors
INVENTOR(S): Orme, Mark W.; Sawyer, Jason Scott; Schultze, Lisa M.; Daugan, Alain Claude-Marie; Gellibert, Francoise
PATENT ASSIGNEE(S): Lilly Icos LLC, USA
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000656	A2	20020103	WO 2001-US15935	20010515
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001061707	A5	20020108	AU 2001-61707	20010515

PRIORITY APPLN. INFO.: US 2000-213647P P 20000623
WO 2001-US15935 W 20010515

OTHER SOURCE(S): MARPAT 136:85828
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

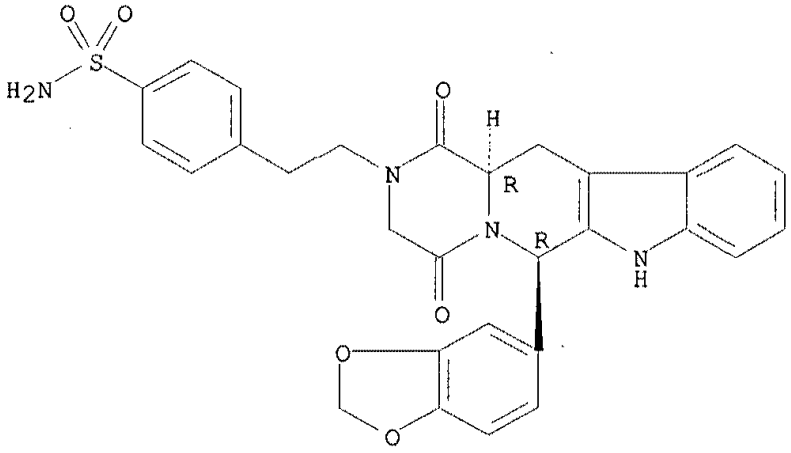
AB The pyrazinopyridoindolediones I (R = halo, C1-6-alkyl; R1 = aryl, heteroaryl, amino, R4O, R4CO, R4SO, R4SO2, C1-4-alkylene-CO2R4, C1-4-alkylenehetreroaryl, sulfamoyl, cyano, NO2, CO-C1-4-alkyleneheteroaryl, C1-4-alkylene-OR4, etc.; R2 = monocyclic arom. ring consisting of benzene, thiophene, furan, and pyridine, and an optionally substituted bicyclic ring wherein the fused ring is a 5- or 6-membered ring comprised of C and optionally heteroatoms selected from O, S, and N; R3 = H, C1-6-alkyl; R4 = H, alkyl, aryl, heteroaryl, etc.) and their salts and solvates were prepd. as cyclic GMP phosphodiesterase inhibitors. Thus, D-tryptophan Me ester hydrochloride was treated with piperonal to give the carbolinecarboxylate II, which was treated with chloroacetyl chloride followed by cyclization with hydroxylamine-HCl to give the pyrazinopyridoindoledione III. The cyclic GMP phosphodiesterase inhibitor IC50 of III 0.0075 .mu.M.

IT **385769-78-8P 385769-80-2P 385769-82-4P**
385769-84-6P 385769-86-8P 385769-88-0P
385769-90-4P 385769-94-8P 385769-98-2P
385770-00-3P 385770-01-4P 385770-03-6P
385770-04-7P 385770-06-9P 385770-07-0P
385770-09-2P 385770-11-6P 385770-13-8P

385770-15-0P 385770-18-3P 385770-20-7P
385770-22-9P 385770-24-1P 385770-26-3P
385770-28-5P 385770-29-6P 385770-30-9P
385770-31-0P 385770-32-1P 385770-34-3P
385770-36-5P 385770-38-7P 385770-40-1P
385770-41-2P 385770-43-4P 385770-44-5P
385770-46-7P 385770-48-9P 385770-49-0P
385770-50-3P 385770-52-5P 385770-54-7P
385770-56-9P 385770-57-0P 385770-58-1P
385770-60-5P 385770-62-7P 385770-64-9P
385770-66-1P 385770-68-3P 385770-70-7P
385770-72-9P 385770-73-0P 385770-75-2P
385770-76-3P 385770-77-4P 385770-78-5P
385770-79-6P 385770-80-9P 385770-82-1P
385770-83-2P 385770-85-4P 385770-89-8P
385770-91-2P 385770-92-3P 385770-93-4P
385770-95-6P 385770-96-7P 385770-98-9P
385770-99-0P 385771-02-8P 385771-03-9P
385771-05-1P 385771-06-2P 385771-08-4P
385771-10-8P
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrazinopyridoindolediones as cyclic GMP phosphodiesterase inhibitors)

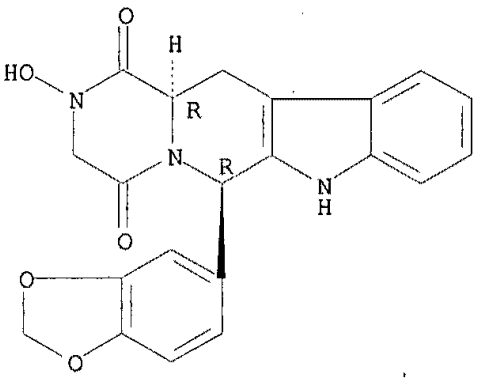
RN 385769-78-8 CAPLUS
CN Benzenesulfonamide, 4-[2-[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



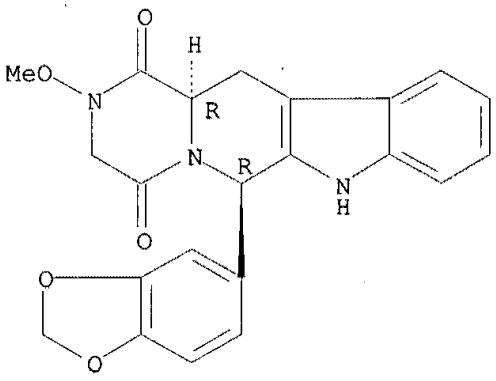
RN 385769-80-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-hydroxy-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



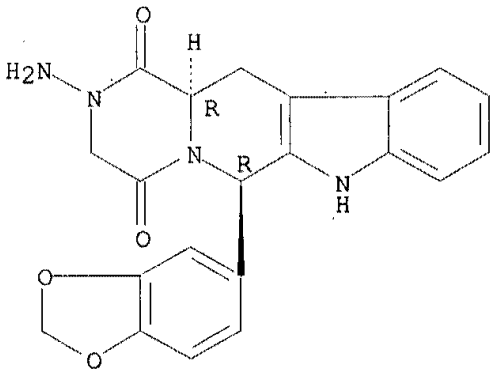
RN 385769-82-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methoxy-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 385769-84-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-amino-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

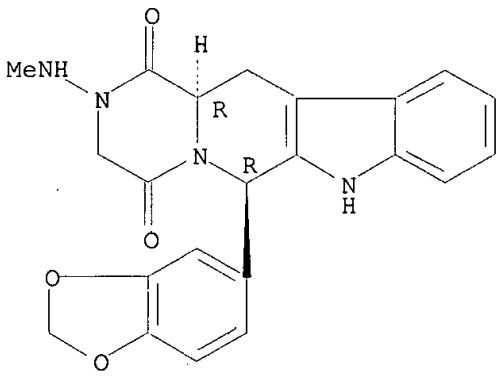
Absolute stereochemistry.



RN 385769-86-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-

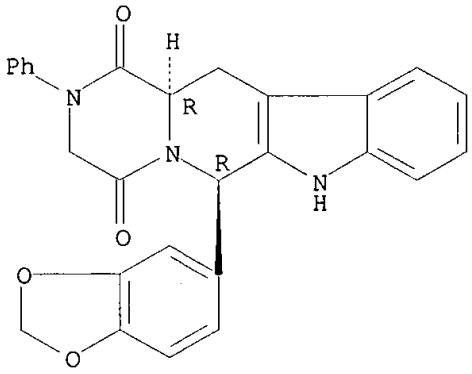
2,3,6,7,12,12a-hexahydro-2-(methylamino)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



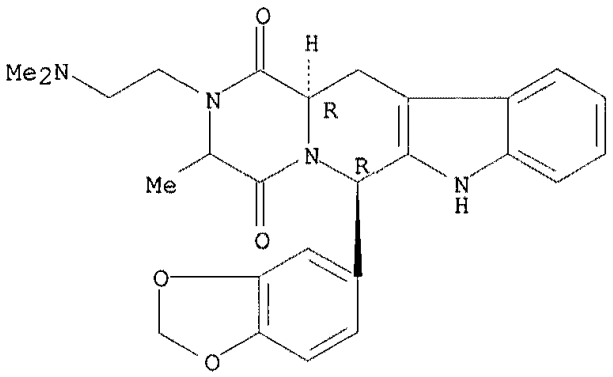
RN 385769-88-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-phenyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



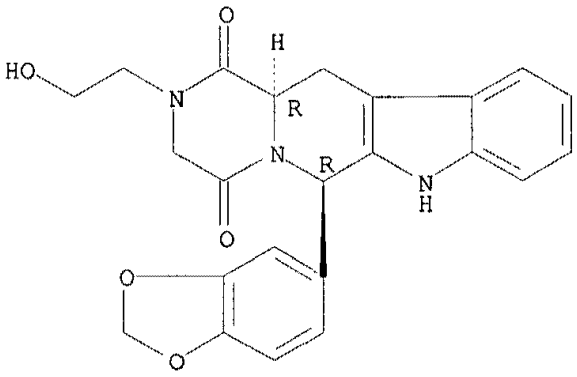
RN 385769-90-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-(dimethylamino)ethyl]-2,3,6,7,12,12a-hexahydro-3-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



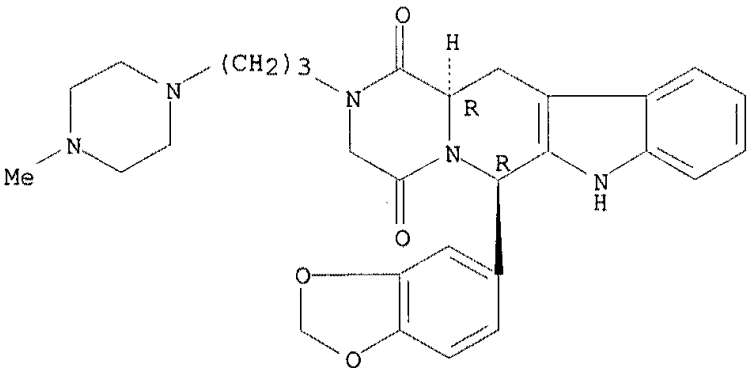
RN 385769-94-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-hydroxyethyl)-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 385769-98-2 CAPLUS
CN 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-[3-(4-methyl-1-piperazinyl)propyl]-, (6R,12aR)-(9CI) (CA INDEX NAME)

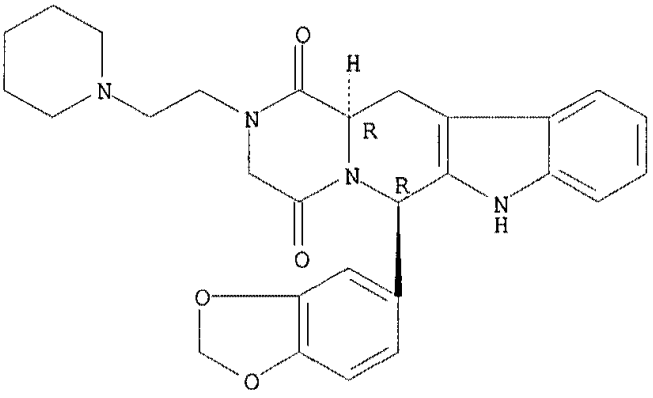
Absolute stereochemistry.



RN 385770-00-3 CAPLUS

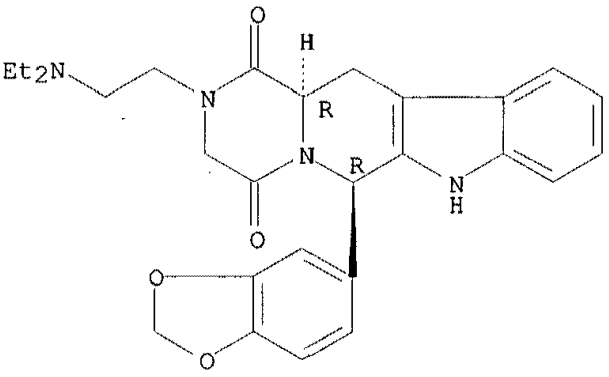
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(1-piperidinyl)ethyl]-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



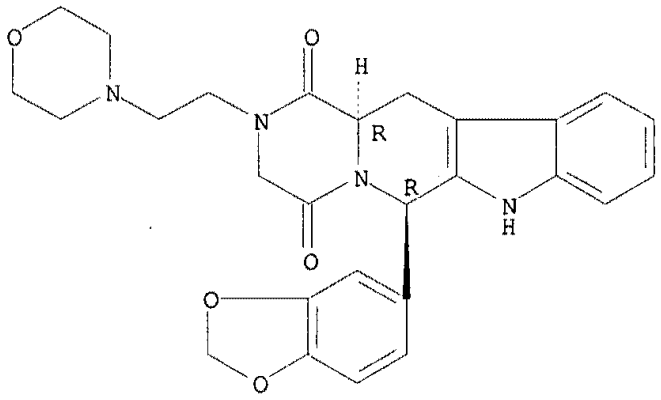
RN 385770-01-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-(diethylamino)ethyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



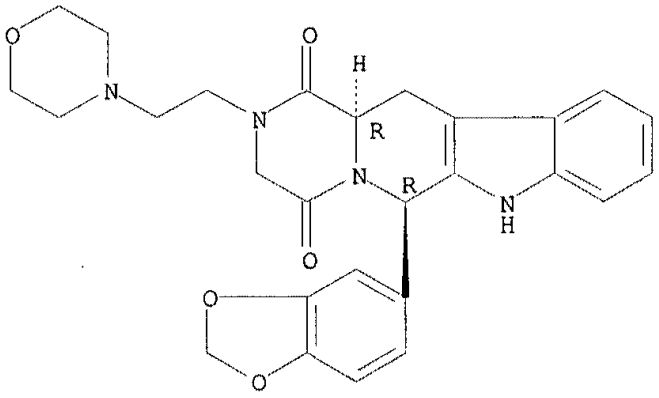
RN 385770-03-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(4-morpholinyl)ethyl]-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



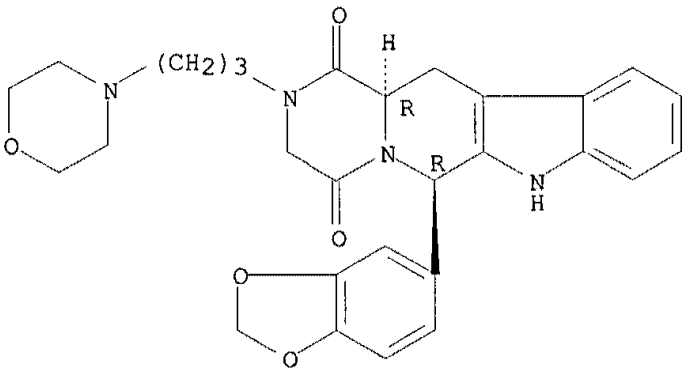
RN 385770-04-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(4-morpholinyl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



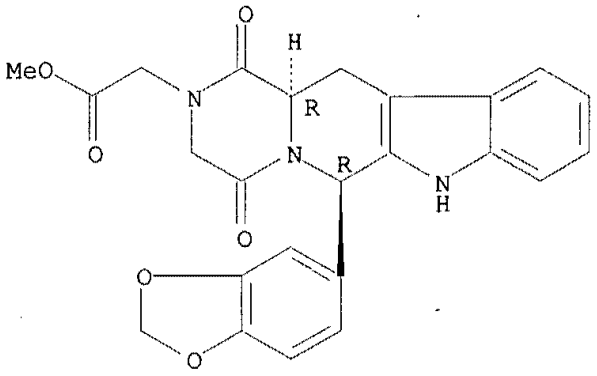
RN 385770-06-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[3-(4-morpholinyl)propyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



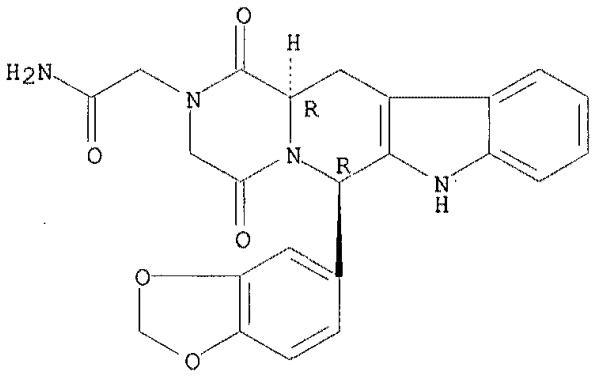
RN 385770-07-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, methyl ester, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



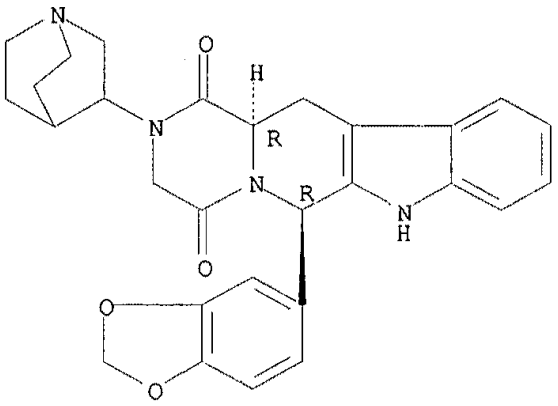
RN 385770-09-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



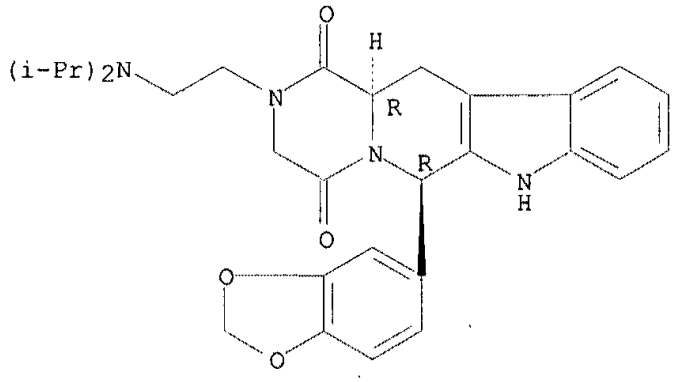
RN 385770-11-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-(1-azabicyclo[2.2.2]oct-3-yl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



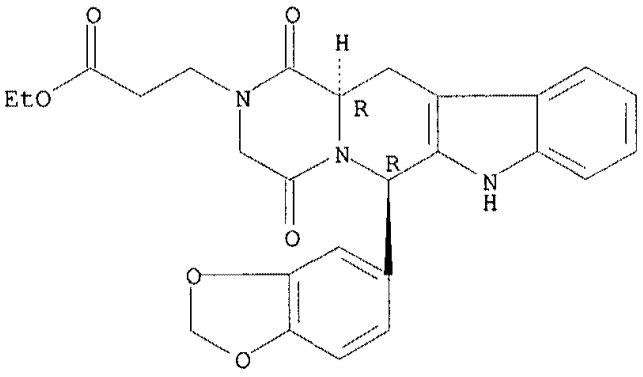
RN 385770-13-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-[bis(1-methylethyl)amino]ethyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



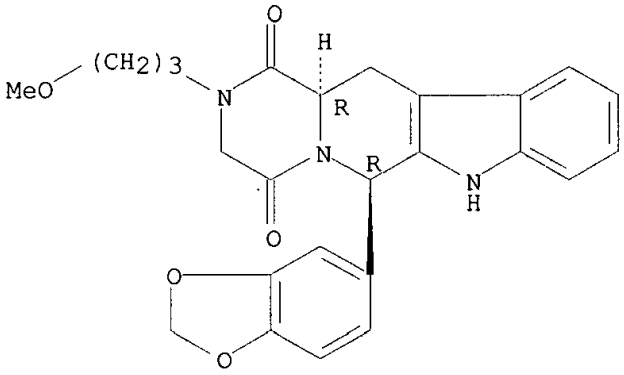
RN 385770-15-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-propanoic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, ethyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



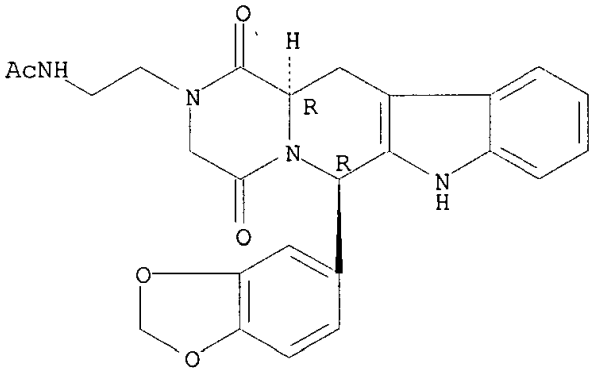
RN 385770-18-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(3-methoxypropyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



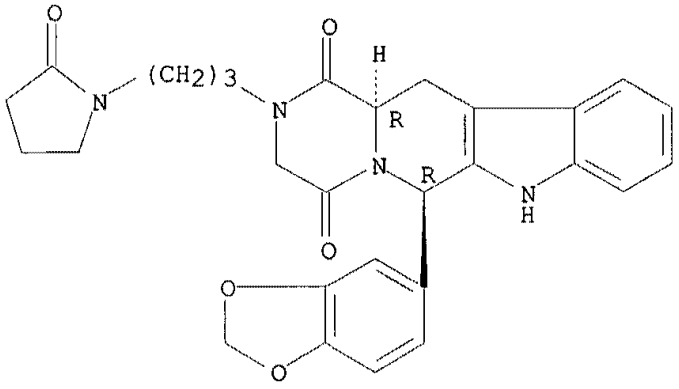
RN 385770-20-7 CAPLUS
CN Acetamide, N-[2-[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]ethyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



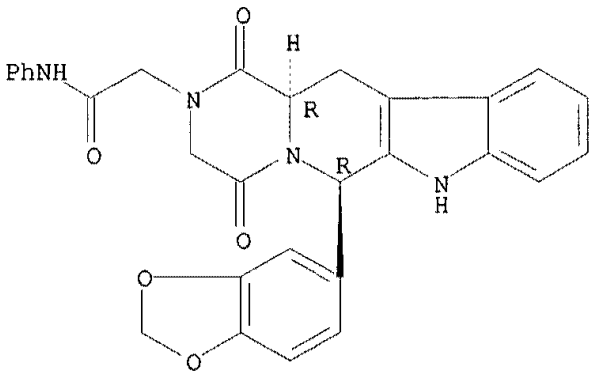
RN 385770-22-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[3-(2-oxo-1-pyrrolidinyl)propyl]-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



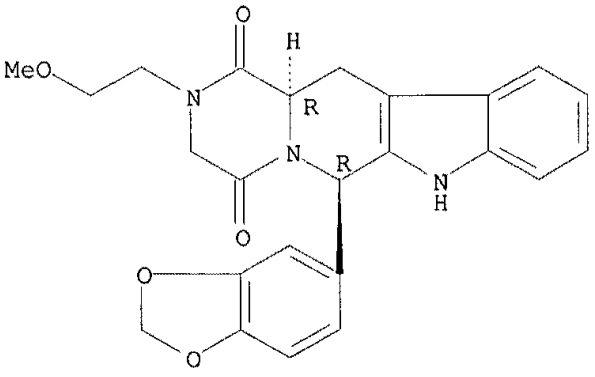
RN 385770-24-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-N-phenyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



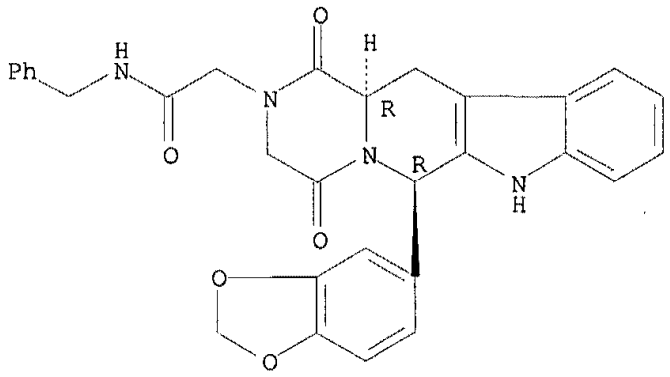
RN 385770-26-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-methoxyethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



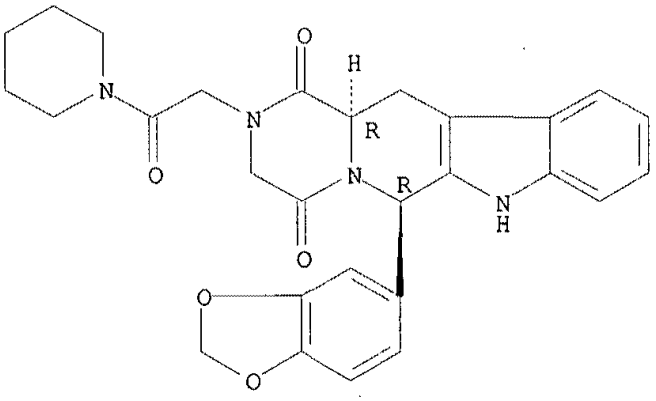
RN 385770-28-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-N-(phenylmethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



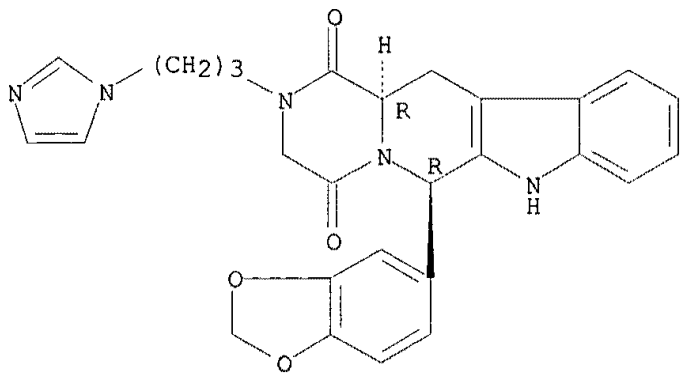
RN 385770-29-6 CAPLUS
CN Piperidine, 1-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



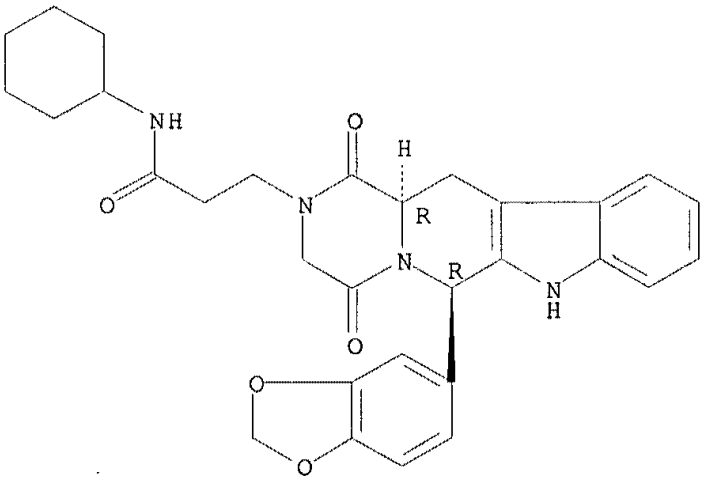
RN 385770-30-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[3-(1H-imidazol-1-yl)propyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



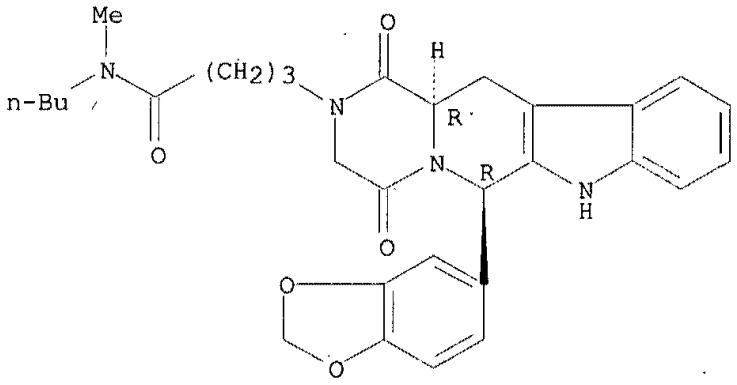
RN 385770-31-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-propanamide, 6-(1,3-benzodioxol-5-yl)-N-cyclohexyl-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



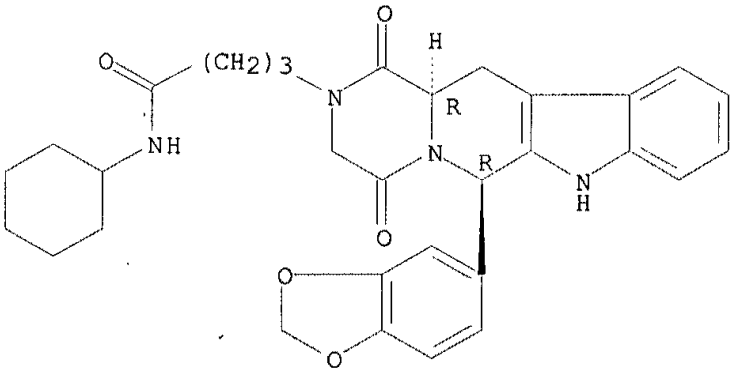
RN 385770-32-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-butanamide, 6-(1,3-benzodioxol-5-yl)-N-butyl-3,4,6,7,12,12a-hexahydro-N-methyl-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



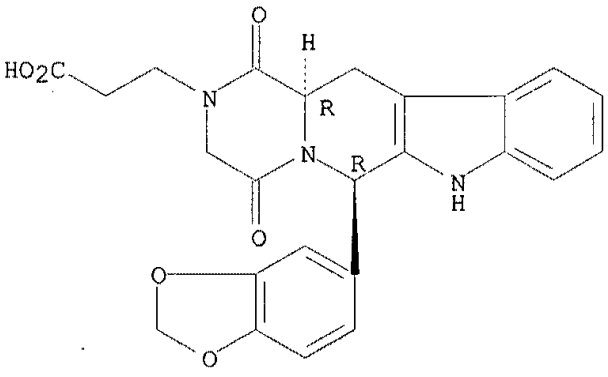
RN 385770-34-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-butanamide, 6-(1,3-benzodioxol-5-yl)-N-cyclohexyl-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



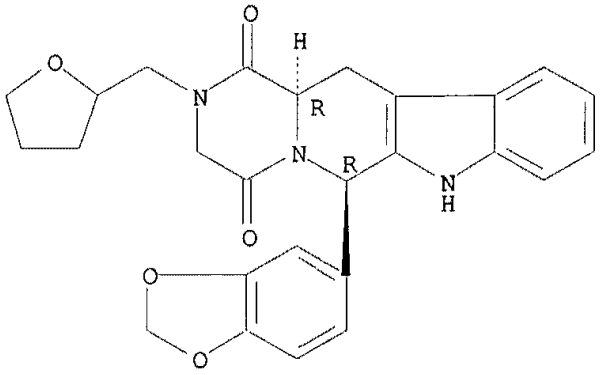
RN 385770-36-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-propanoic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



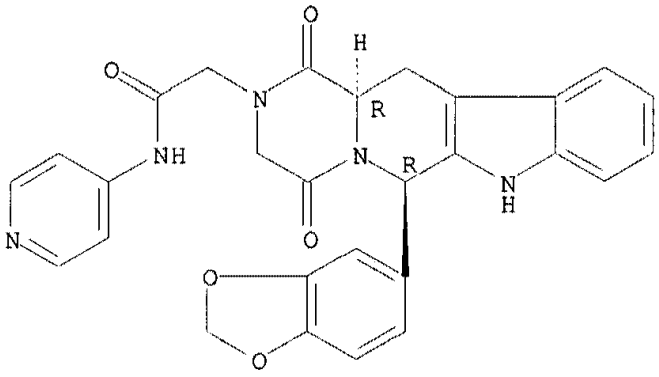
RN 385770-38-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[(tetrahydro-2-furanyl)methyl]-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



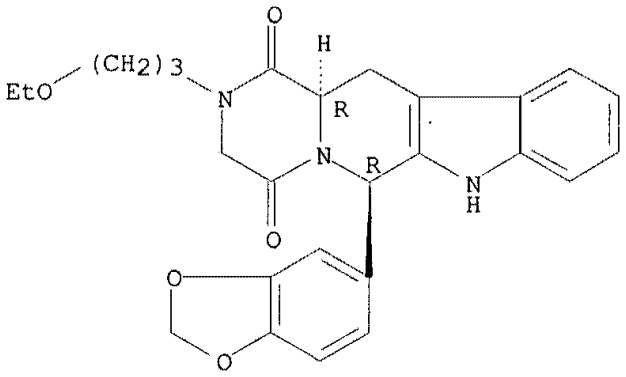
RN 385770-40-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-N-4-pyridinyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



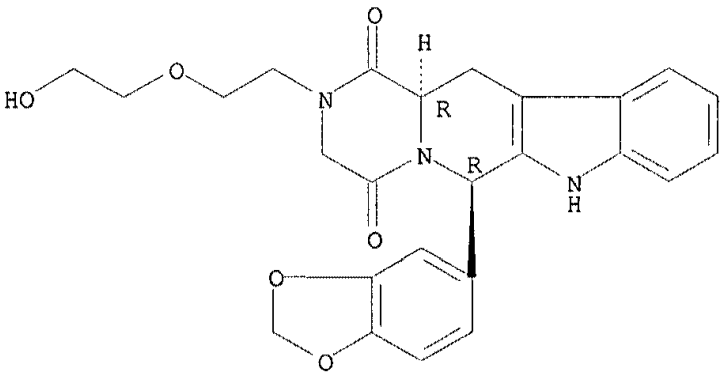
RN 385770-41-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(3-ethoxypropyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



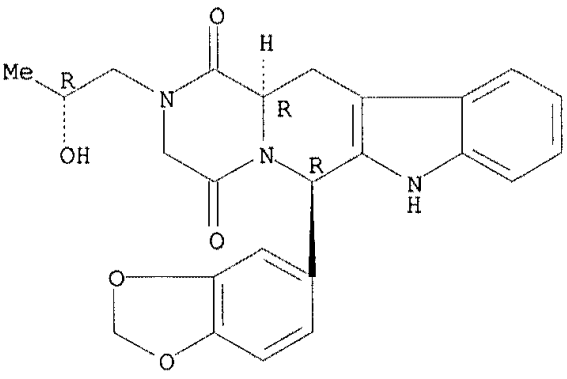
RN 385770-43-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(2-hydroxyethoxy)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 385770-44-5 CAPLUS
CN 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-[(2R)-2-hydroxypropyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

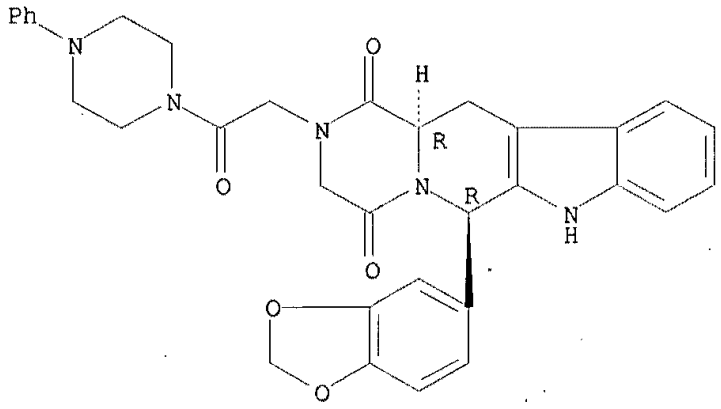
Absolute stereochemistry.



RN 385770-46-7 CAPLUS

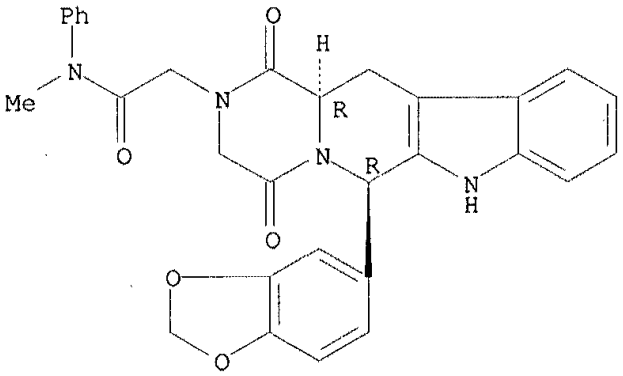
CN Piperazine, 1-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]acetyl]-4-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



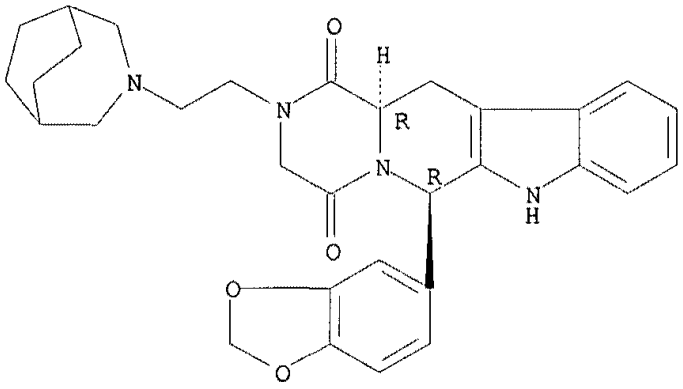
RN 385770-48-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-N-methyl-1,4-dioxo-N-phenyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



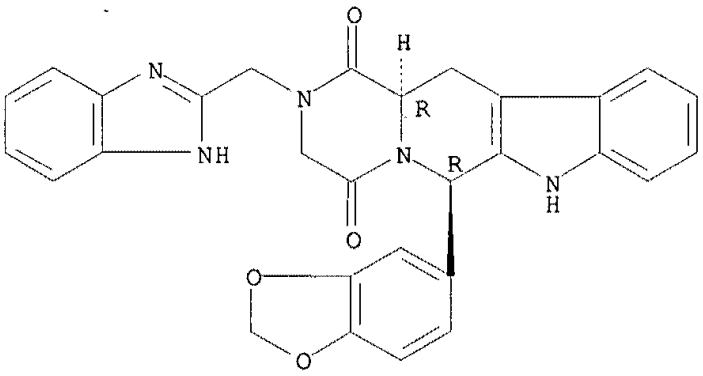
RN 385770-49-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-[2-(3-azabicyclo[3.2.2]non-3-yl)ethyl]-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



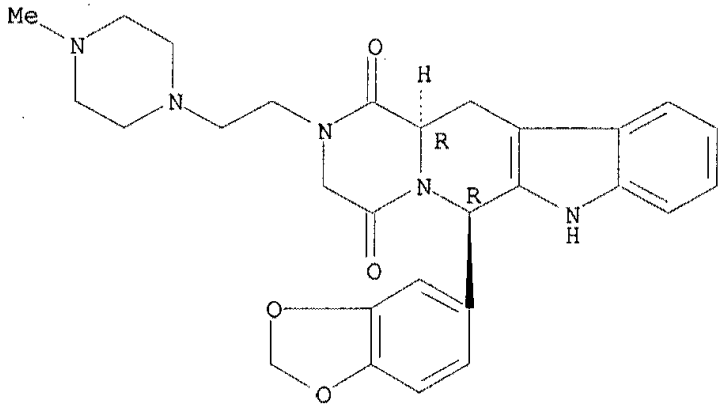
RN 385770-50-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-(1H-benzimidazol-2-ylmethyl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



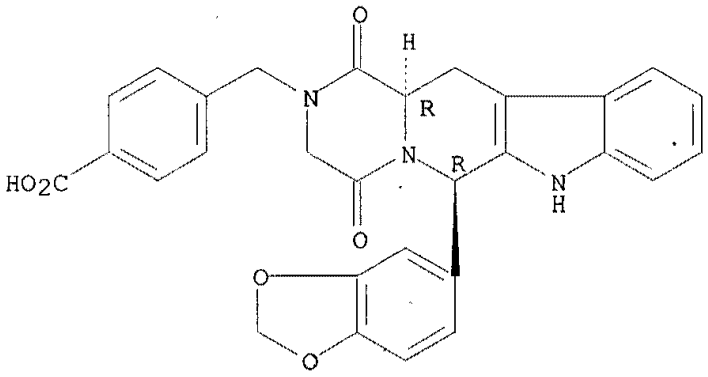
RN 385770-52-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(4-methyl-1-piperazinyl)ethyl]-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



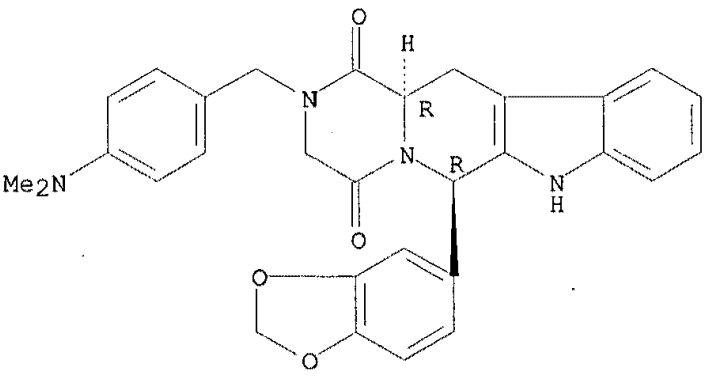
RN 385770-54-7 CAPLUS
CN Benzoic acid, 4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



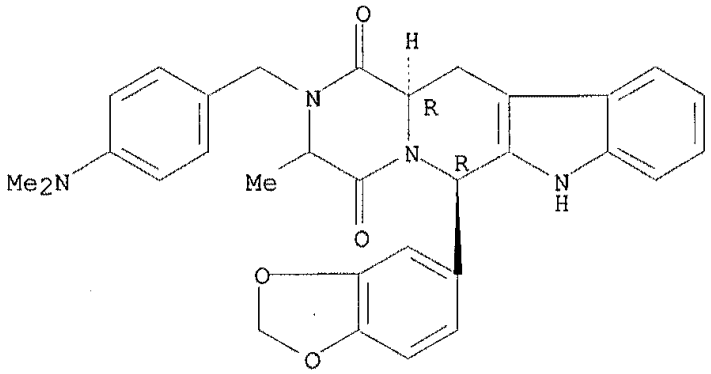
RN 385770-56-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[[4-(dimethylamino)phenyl]methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



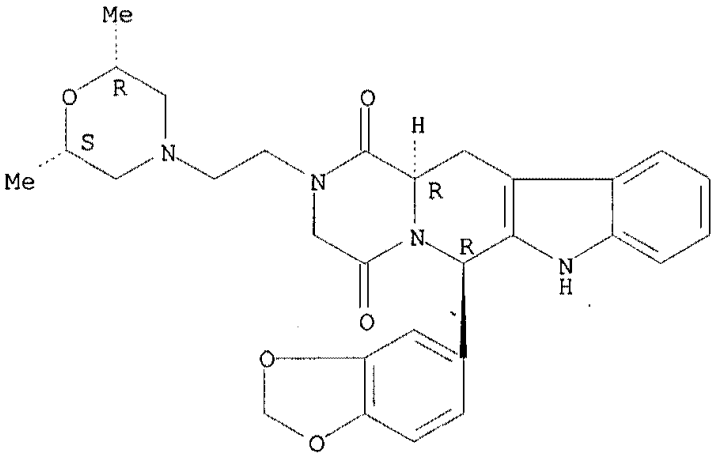
RN 385770-57-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[[4-(dimethylamino)phenyl]methyl]-2,3,6,7,12,12a-hexahydro-3-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



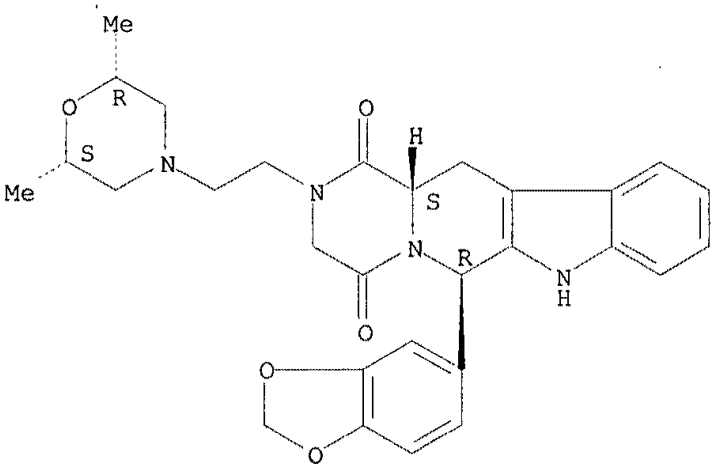
RN 385770-58-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-[(2R,6S)-2,6-dimethyl-4-morpholinyl]ethyl]-2,3,6,7,12,12a-hexahydro-, (6S,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



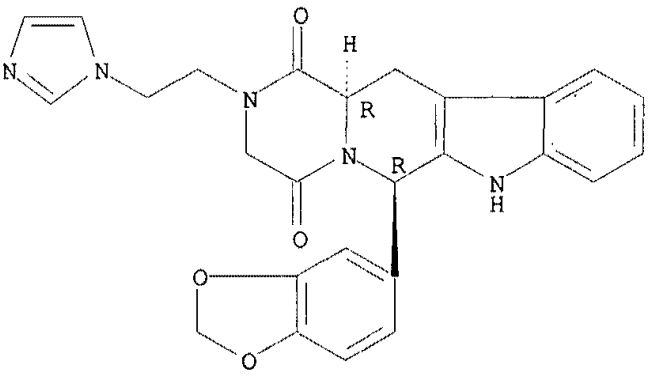
RN 385770-60-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-[(2R,6S)-2,6-dimethyl-4-morpholinyl]ethyl]-2,3,6,7,12,12a-hexahydro-, (6S,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



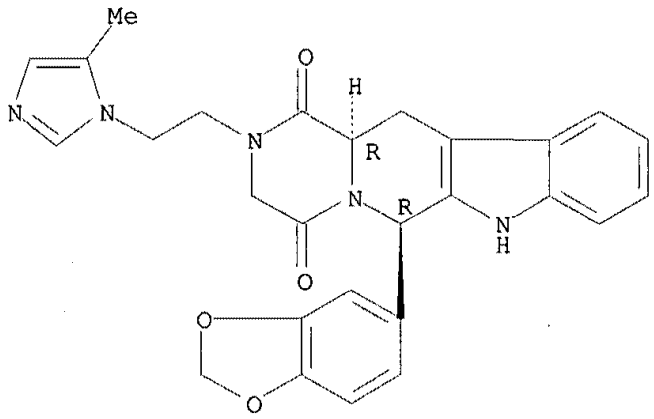
RN 385770-62-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(1H-imidazol-1-yl)ethyl]-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



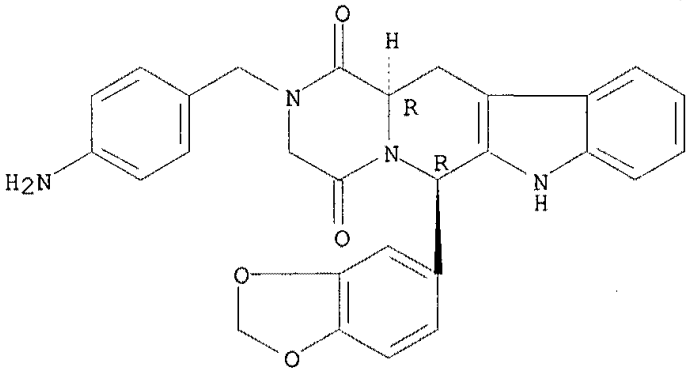
RN 385770-64-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(5-methyl-1H-imidazol-1-yl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



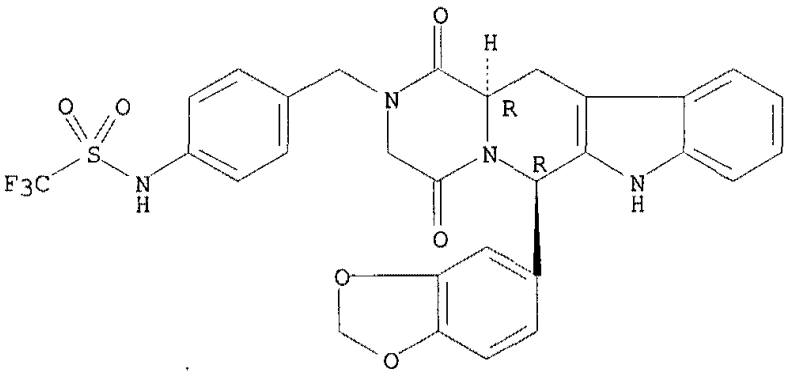
RN 385770-66-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-[(4-aminophenyl)methyl]-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



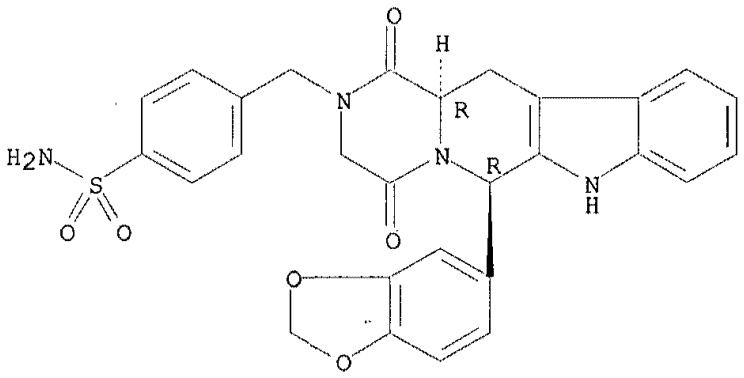
RN 385770-68-3 CAPLUS
CN Methanesulfonamide, N-[4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]phenyl]-1,1,1-trifluoro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



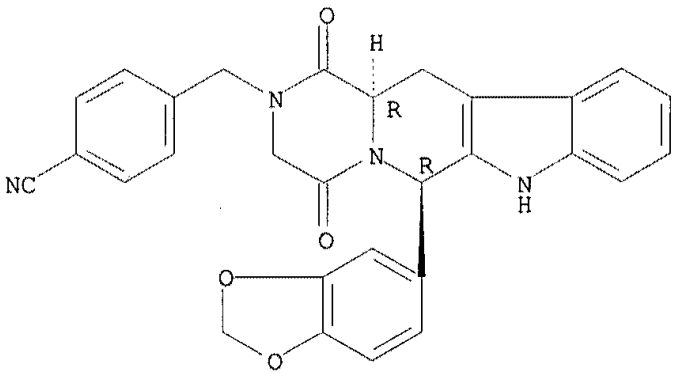
RN 385770-70-7 CAPLUS
CN Benzenesulfonamide, 4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



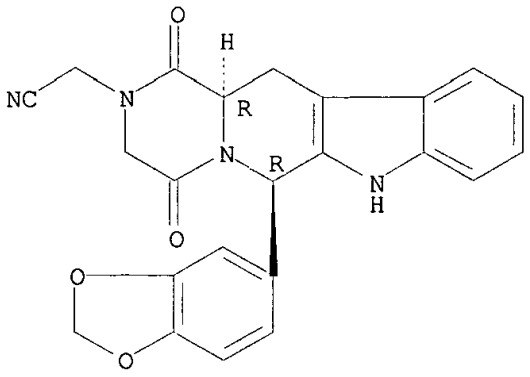
RN 385770-72-9 CAPLUS
CN Benzonitrile, 4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



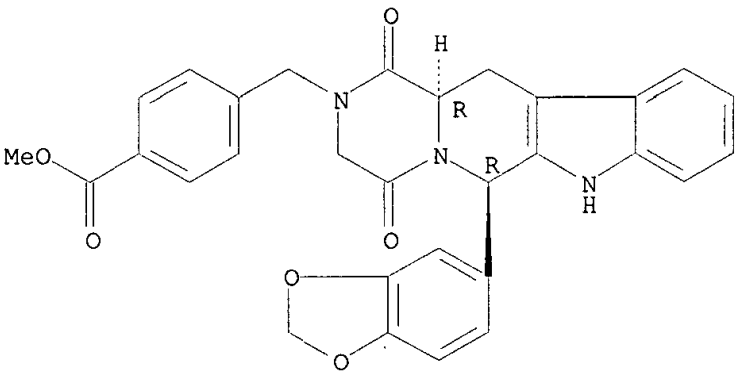
RN 385770-73-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetonitrile, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



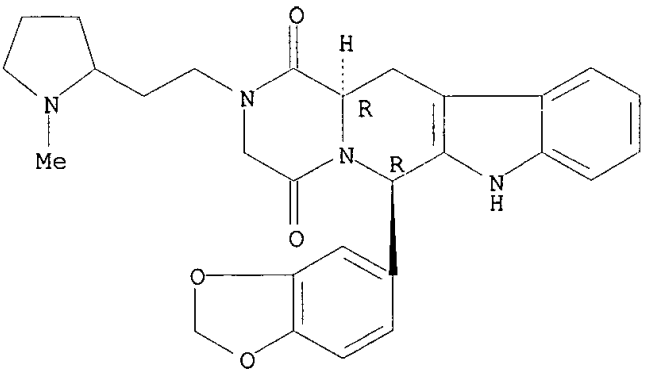
RN 385770-75-2 CAPLUS
CN Benzoic acid, 4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 385770-76-3 CAPLUS
CN 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-[2-(1-methyl-2-pyrrolidinyl)ethyl]-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

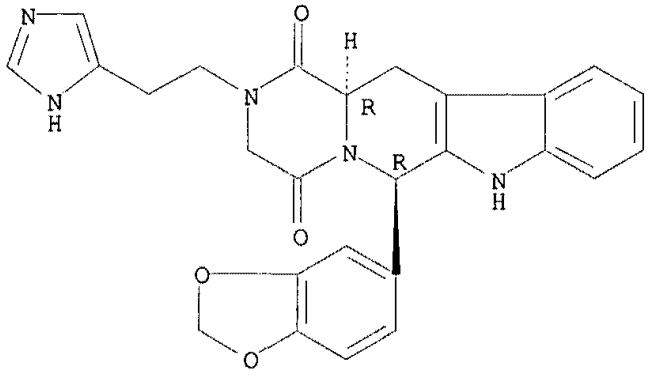
Relative stereochemistry.



RN 385770-77-4 CAPLUS

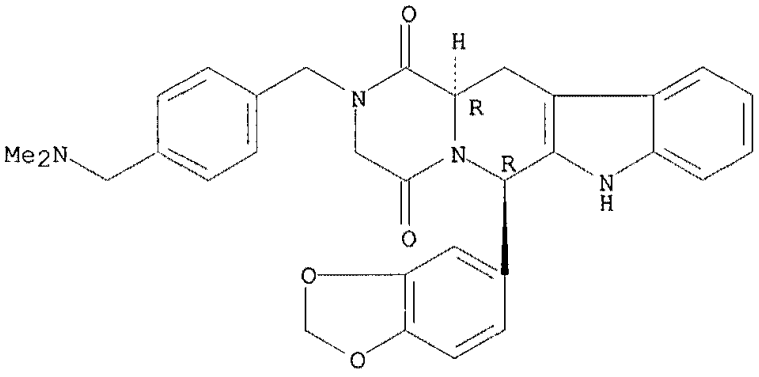
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(1H-imidazol-4-yl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



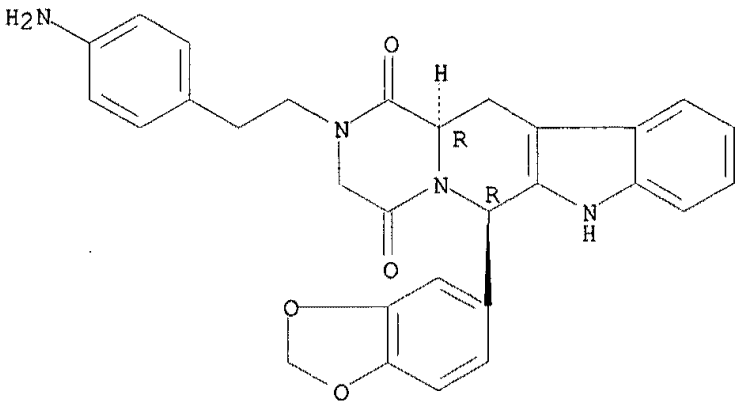
RN 385770-78-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[[4-[(dimethylamino)methyl]phenyl]methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



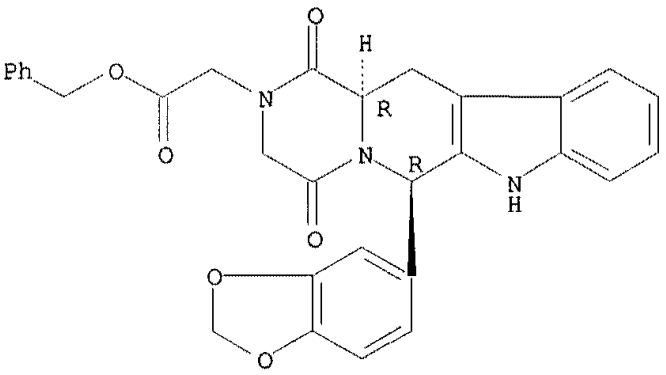
RN 385770-79-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-[2-(4-aminophenyl)ethyl]-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



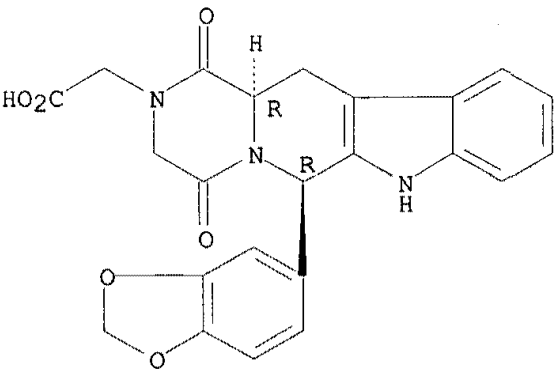
RN 385770-80-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, phenylmethyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



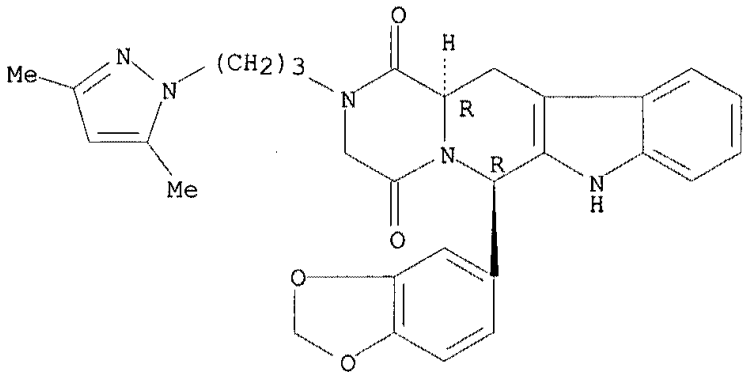
RN 385770-82-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



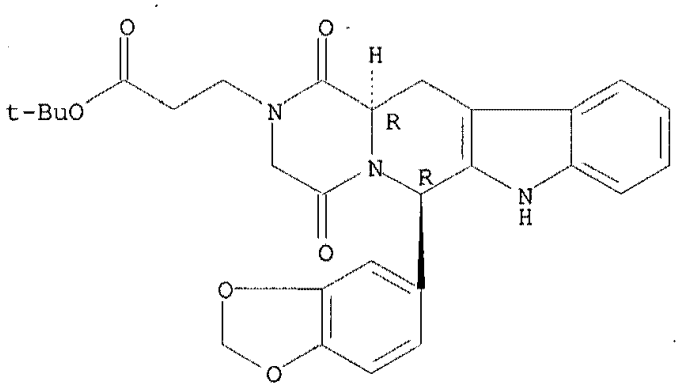
RN 385770-83-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[3-(3,5-dimethyl-1H-pyrazol-1-yl)propyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



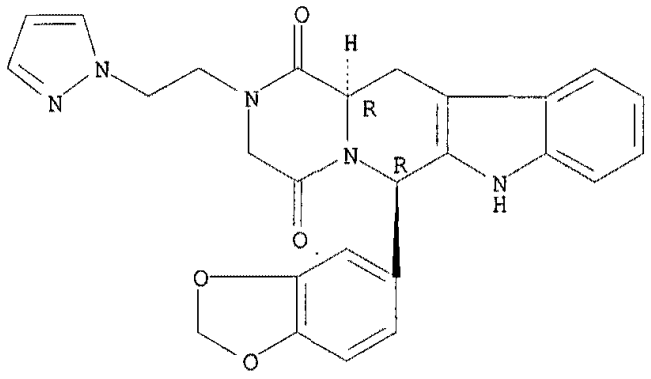
RN 385770-85-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-propanoic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, 1,1-dimethylethyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



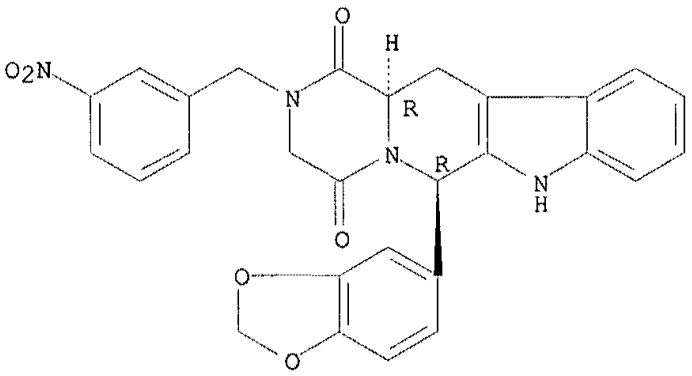
RN 385770-89-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(1H-pyrazol-1-yl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



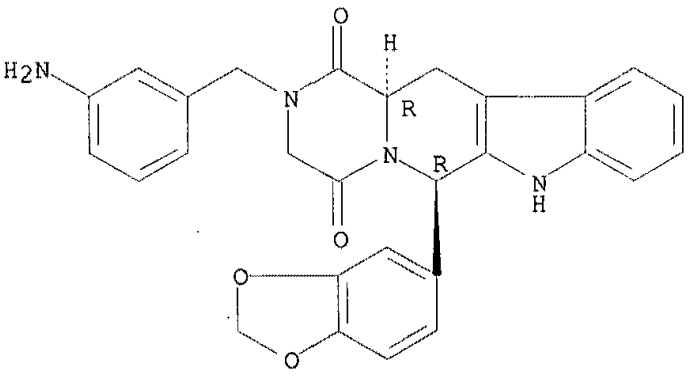
RN 385770-91-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[(3-nitrophenyl)methyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 385770-92-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-[(3-aminophenyl)methyl]-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

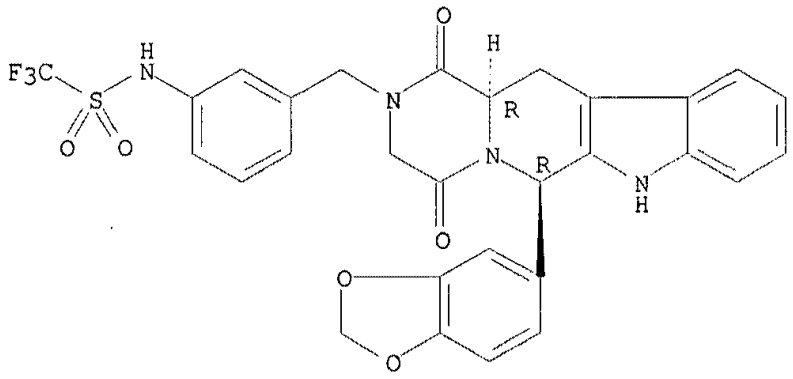
Absolute stereochemistry.



RN 385770-93-4 CAPLUS

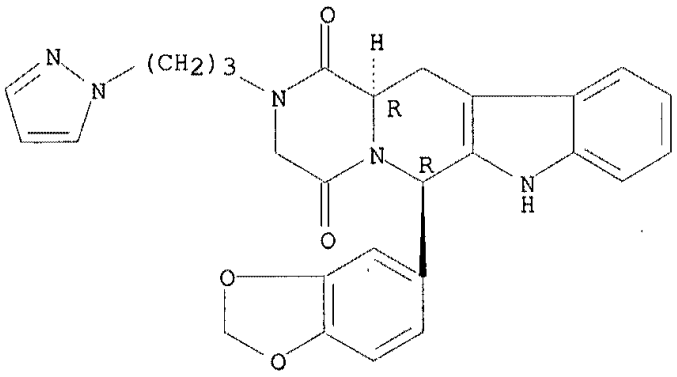
CN Methanesulfonamide, N-[3-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]phenyl]-1,1,1-trifluoro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



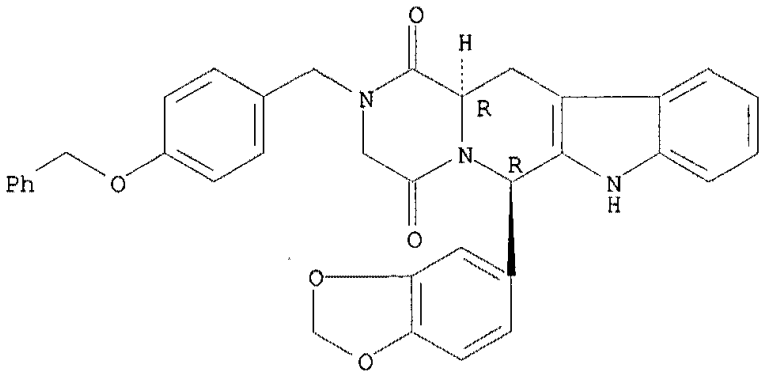
RN 385770-95-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[3-(1H-pyrazol-1-yl)propyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



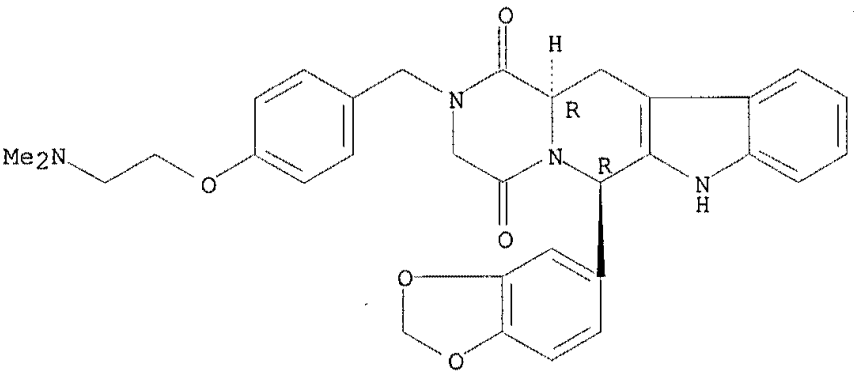
RN 385770-96-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[[4-(phenylmethoxy)phenyl]methyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



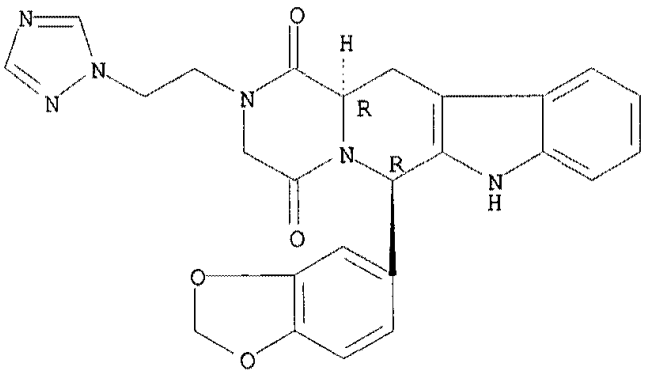
RN 385770-98-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 385770-99-0 CAPLUS
CN 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-[2-(1H-1,2,4-triazol-1-yl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

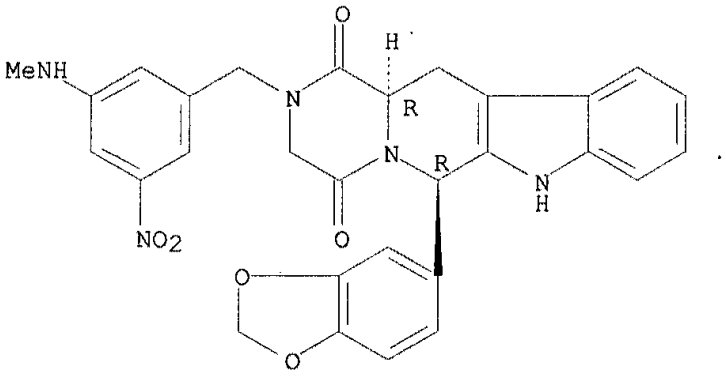
Absolute stereochemistry.



RN 385771-02-8 CAPLUS

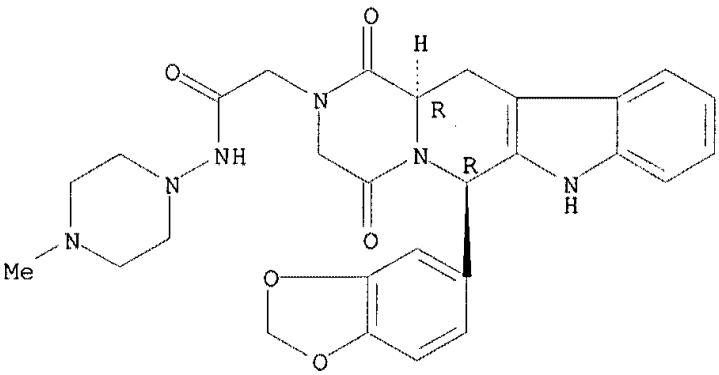
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[[3-(methylamino)-5-nitrophenyl]methyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



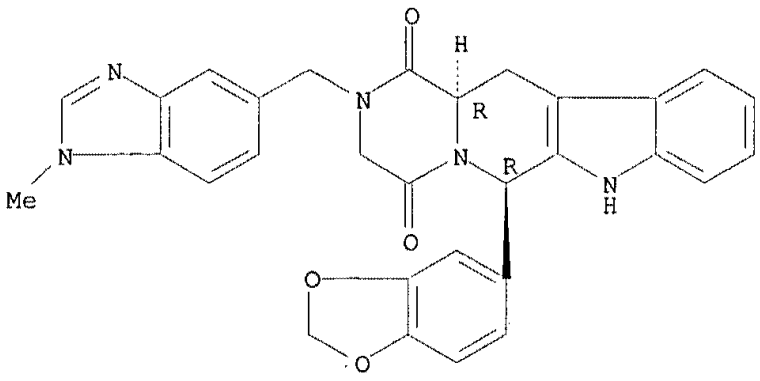
RN 385771-03-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-N-(4-methyl-1-piperazinyl)-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



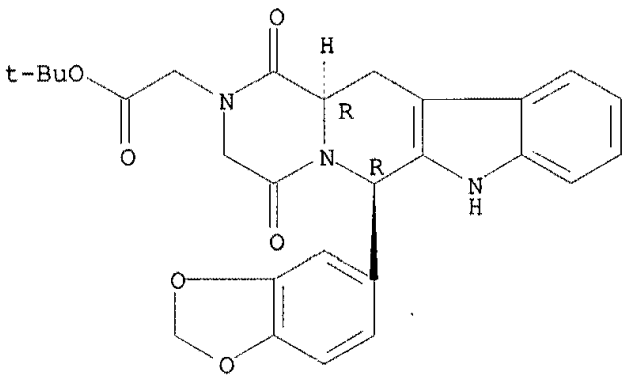
RN 385771-05-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[(1-methyl-1H-benzimidazol-5-yl)methyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



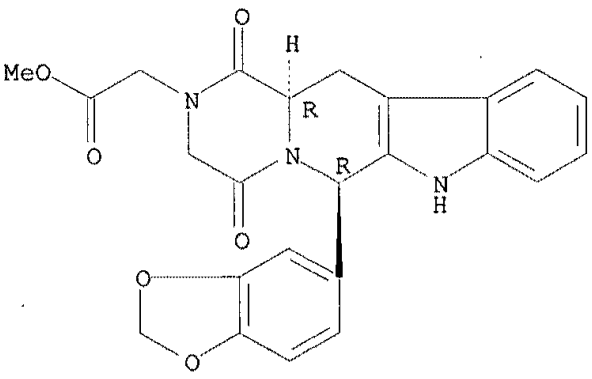
RN 385771-06-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, 1,1-dimethylethyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 385771-08-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, methyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

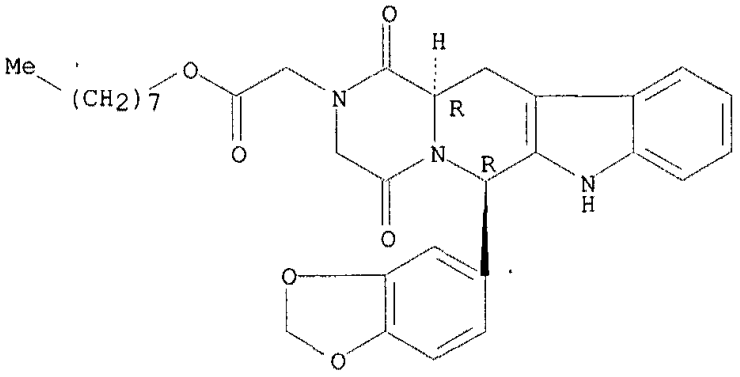
Absolute stereochemistry.



RN 385771-10-8 CAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, octyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 11 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:924320 CAPLUS
DOCUMENT NUMBER: 136:31728
TITLE: Daily treatment for erectile dysfunction using a phosphodiesterase 5 (PDE5) inhibitor
INVENTOR(S): Whitaker, John S.; Saenz de Tejada, Inigo; Ferguson, Kenneth M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No. 558,911.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001053780	A1	20011220	US 2001-834442	20010413
EP 1173181	A2	20020123	EP 2000-926367	20000426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001005275	A	20011206	NO 2001-5275	20011029

PRIORITY APPLN. INFO.: US 1999-132036P P 19990430
US 2000-558911 A2 20000426
WO 2000-US11129 W 20000426

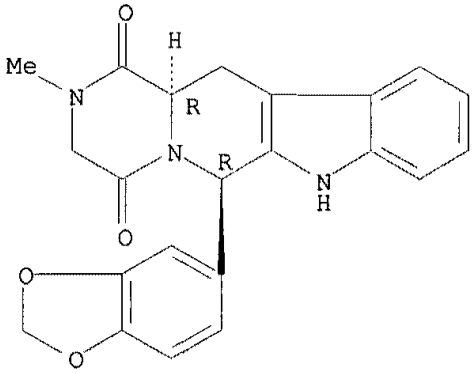
AB The invention provides phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manuf. In particular, the invention provides potent inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase type 5 (PDE5) that, when incorporated into a pharmaceutical product at about 1-10 mg unit dosage, are useful for the treatment of sexual dysfunction by daily administration of the PDE5 inhibitor. The articles of manuf. described are characterized by PDE5 inhibition, and accordingly, provide a benefit in therapeutic areas where inhibition of PDE5 is desired, esp. erectile dysfunction, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes and with an improvement of vascular conditioning.

IT **171596-29-5 171596-40-0**

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase 5 inhibitor for daily treatment for erectile dysfunction)

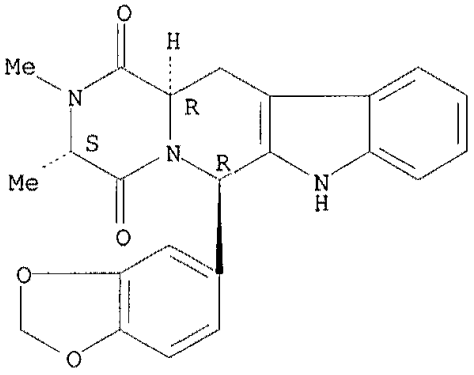
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-40-0 CAPLUS
CN 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-2,3-dimethyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L12 ANSWER 12 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:916407 CAPLUS
DOCUMENT NUMBER: 136:53755
TITLE: Synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction
INVENTOR(S): Garvey, David S.; Saenz de Tejada, Inigo; Earl, Richard A.; Khanapure, Subhash P.
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: U.S., 117 pp., Cont.-in-part of U.S. 5,958,926.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6331543	B1	20011218	US 1999-387727	19990901
US 5874437	A	19990223	US 1996-740764	19961101
WO 9819672	A1	19980514	WO 1997-US19870	19971031
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5958926	A	19990928	US 1998-145142	19980901
US 2002019405	A1	20020214	US 2001-941691	20010830

PRIORITY APPLN. INFO.: US 1996-740764 A2 19961101
WO 1997-US19870 A2 19971031
US 1998-145142 A2 19980901
US 1999-387727 A1 19990901

OTHER SOURCE(S): MARPAT 136:53755
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

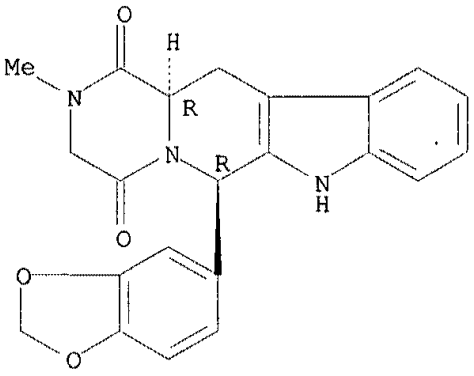
AB Compds. I-V, derivs. thereof, and certain substituted Ph and phthalzaine derivs. were claimed [D2 = H, alkyl, D; D = NO, NO2, alkyl, acyl, phosphoryl, silyl, etc.; A1-3 comprise the other subunits of a 5- or 6-membered monocyclic arom. ring; R8 = H, (halo)alkyl; p = 1-10; R24 = H, cyclohexyl, piperidinyl, etc., with the proviso that at least one of A1-3, J, or R24 contains T-Q or D; T = bond, O, S(O), amino; Q = NO, NO2; D1 = D or H; R37 = (hetero)aryl; R38 = H, halo, alkyl; G1 = alkyl, alkenyl or is part of a ring fused to the piperidine moiety of III; G4 = O, S; R40 = H, alkyl, haloalkyl, halo, etc.; R41 = alkyl, hydroxyalkyl, alkylcarboxy, etc.; R42 = aryl, alkylaryl, alkyloxyaryl; T1 = alkyl, oxyalkyl, thioalkyl, aminoalkyl]. Two synthetic examples were provided. E.g., the S-nitroso deriv. of the 3-mercapto-3-methylbutyric acid ester of dipyridamole (VI) was prepd. in 4 steps from dipyridamole in 3.5% overall yield. VI at doses of 10 and 30 .mu.M was more efficacious in relaxing phenylephrine-induced tissue contraction than was the known phosphodiesterase inhibitor, dipyridamole. The present invention describes novel (nitrosated/nitrosylated) phosphodiesterase inhibitors, and compns. contg. at least one (nitrosated/nitrosylated) phosphodiesterase inhibitor, and, optionally, one or more compds. that donate, transfer or release NO, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of NO, or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides methods for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females, and for treating or preventing diseases induced by the increased metab. of cGMP, such as hypertension, pulmonary hypertension, etc.

IT **171596-29-5D**, ICOS 351, nitroso derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



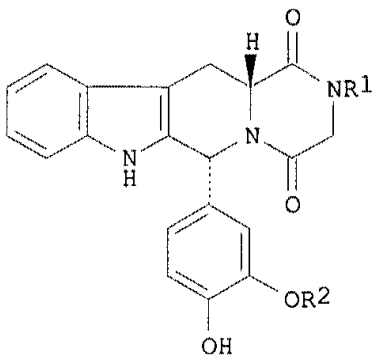
REFERENCE COUNT: 86 THERE ARE 86 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:904172 CAPLUS
DOCUMENT NUMBER: 136:20091
TITLE: Preparation of tetracyclic diketopiperazine compounds as PDE5 inhibitor
INVENTOR(S): Orme, Mark W.; Daugan, Alain Claude-Marie; Bombrun, Agnes
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001094347	A1	20011213	WO 2001-US15937	20010515

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-210324P P 20000608
OTHER SOURCE(S): MARPAT 136:20091
GI



I

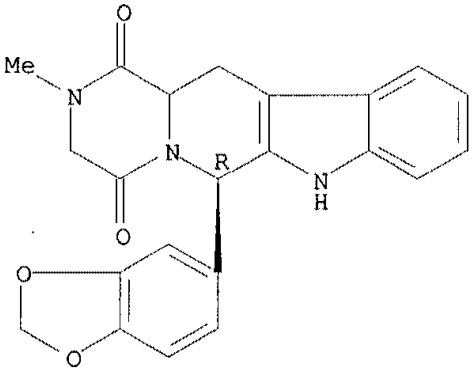
AB The title compds. I [R1 = C1-6 alkyl; R2 = H, Me] were prepd. and use of the compds. as PDE5 inhibitors was described.. E.g., (6R,12aR)-6-(3,4-dihydroxyphenyl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione was prepd. I may be used for male erectile dysfunction or female arousal disorder.

IT **378788-17-1P**
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of tetracyclic diketopiperazine compds. as PDE5 inhibitor)

RN 378788-17-1 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:904168 CAPLUS
DOCUMENT NUMBER: 136:20090
TITLE: Preparation of cyclic guanosine monophosphate specific phosphodiesterase inhibiting heterocyclylpyrazinopyridoindolediones for treatment of cardiovascular disorders and erectile disfunction
INVENTOR(S): Orme, Mark W.; Sawyer, Jason Scott; Daugan, Alain Claud-Marie
PATENT ASSIGNEE(S): Lilly Icos LLC, USA
SOURCE: PCT Int. Appl., 103 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001094345	A2	20011213	WO 2001-US15936	20010515

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-210137P P 20000607
OTHER SOURCE(S): MARPAT 136:20090
GI

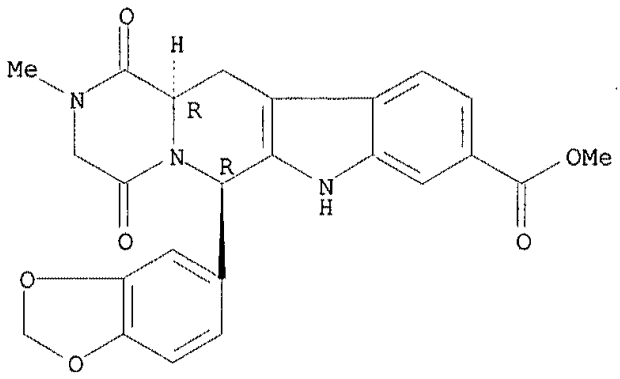
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The pyrazinopyridoindolediones I [R1 = H, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocycloalkyl, etc; R2 = (un)substituted Ph, thienyl, furanyl, pyridyl, bicyclic ring optionally contg. O, S, N hetero atoms, e.g. benzodioxolyl; R3 = H, alkyl; R4 = aryl, heteroaryl, cycloalkyl, acyl, acyloxy, alkoxycarbonyl, aminoalkyl, carbamoyl, alkoxy, amino, acylamino, nitro, cyano, alkylthio etc.; R5 = H, halo, alkyl; R4R5 = 5-, 6-, 7-membered ring optionally contg. O, S, N atoms; m = 1, 2, 3] and their diastereoisomers and pharmaceutically acceptable salts were prepd., possessed cGMP specific phosphodiesterase inhibiting activity, and were useful in the treatment of various cardiovascular disorders, erectile disfunction, and female sexual arousal disorder. Thus, the Me ester of 5-hydroxytryptophan condensed with piperonal in trifluoroacetic acid/CH2Cl2 to give the [(methylenedioxy)phenyl]pyridoindole II which was acylated by ClCH2COCl and then cyclized with MeNH2 to give the [(methylenedioxy)phenyl]hexahydropyrazinopyridoindoledione III that inhibited cGMP specific phosphodiesterase in vitro with an IC50 of 48.1 nM.

IT **379234-97-6P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of (benzodioxolyl)pyrazinopyridoindolediones with cGMP-specific phosphodiesterase inhibiting activity useful in treating cardiovascular, erectile, and female sexual arousal disorders)

RN 379234-97-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-9-carboxylic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-2-methyl-1,4-dioxo-, methyl ester, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

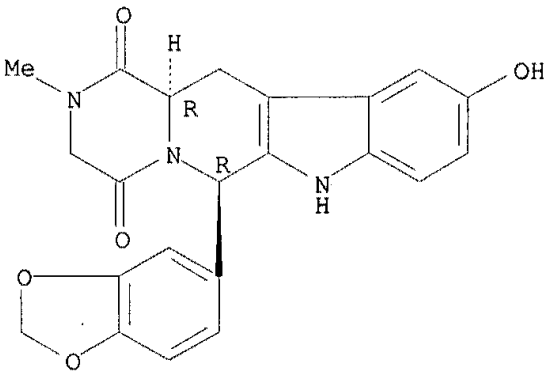
Relative stereochemistry.



IT **379234-74-9P 379234-78-3P 379234-82-9P**
379234-88-5P 379234-98-7P 379235-06-0P
379235-11-7P 379235-12-8P 379235-13-9P
379235-14-0P 379235-15-1P 379235-16-2P
379235-17-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (benzodioxolyl)pyrazinopyridoindolediones with cGMP-specific phosphodiesterase inhibiting activity useful in treating cardiovascular, erectile, and female sexual arousal disorders)

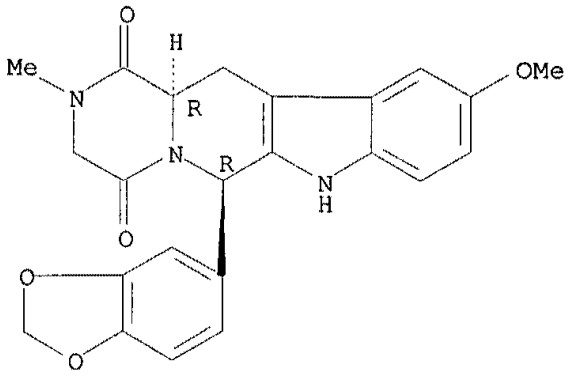
RN 379234-74-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-10-hydroxy-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



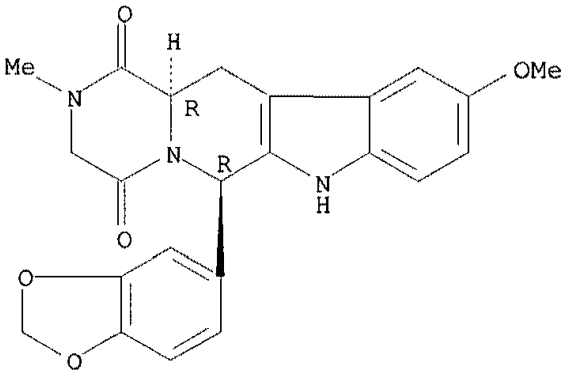
RN 379234-78-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-10-methoxy-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



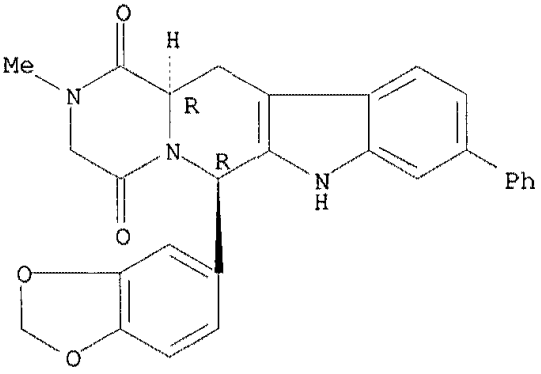
RN 379234-82-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-10-methoxy-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 379234-88-5 CAPLUS
CN 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-9-phenyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

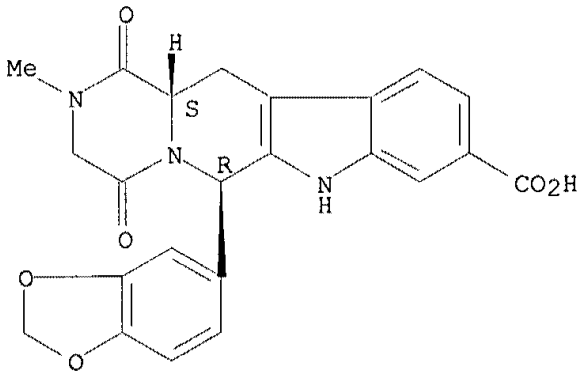
Relative stereochemistry.



RN 379234-98-7 CAPLUS

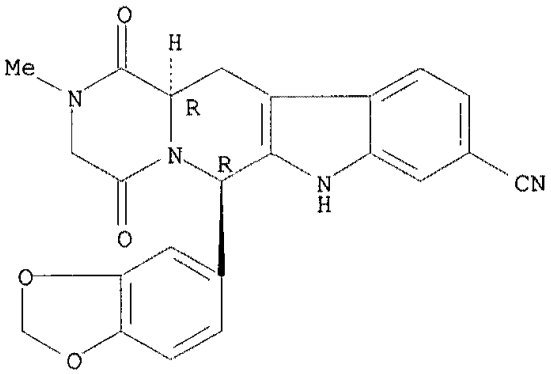
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-9-carboxylic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-2-methyl-1,4-dioxo-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



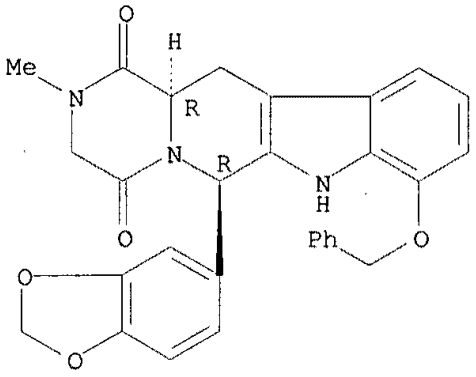
RN 379235-06-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-9-carbonitrile, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-2-methyl-1,4-dioxo-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



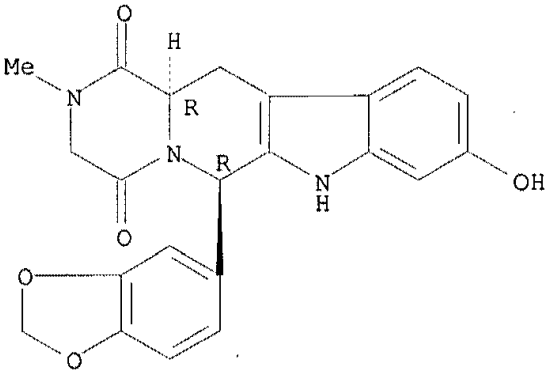
RN 379235-11-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-8-(phenylmethoxy)-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



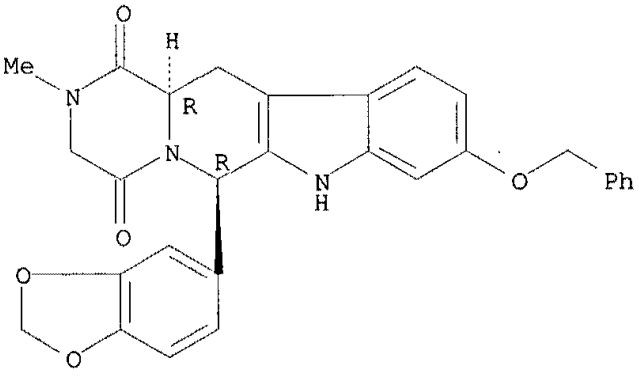
RN 379235-12-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-9-hydroxy-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 379235-13-9 CAPLUS
CN 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-9-(phenylmethoxy)-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

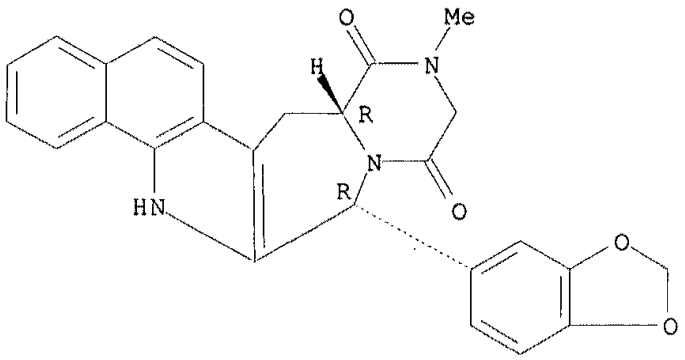
Relative stereochemistry.



RN 379235-14-0 CAPLUS

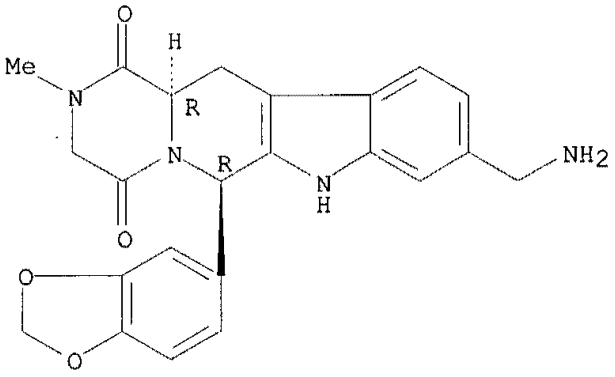
CN Benzo[g]pyrazino[1',2':1,6]pyrido[3,4-b]indole-8,11-dione, 13-(1,3-benzodioxol-5-yl)-7,7a,9,10,13,14-hexahydro-9-methyl-, (7aR,13R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



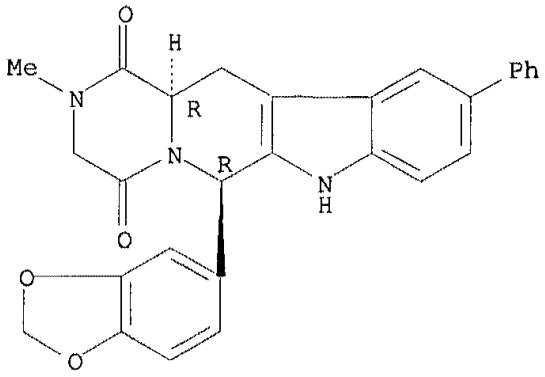
RN 379235-15-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 9-(aminomethyl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



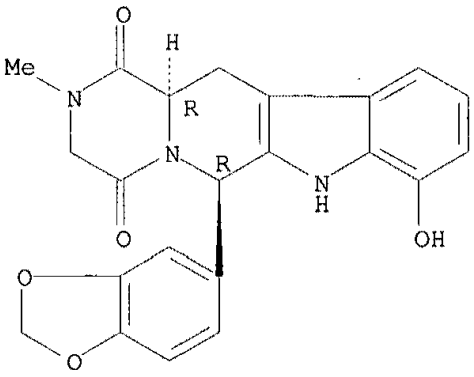
RN 379235-16-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-10-phenyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



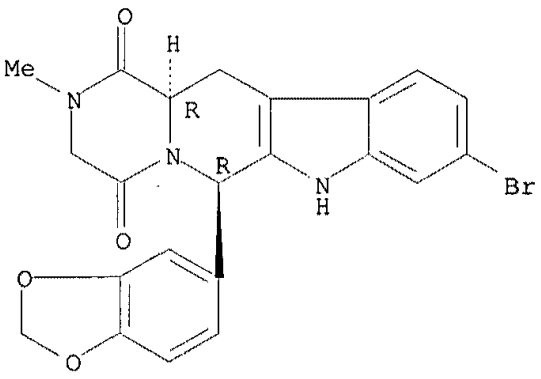
RN 379235-17-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-8-hydroxy-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **379234-87-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of (benzodioxolyl)pyrazinopyridoindolediones with cGMP-specific phosphodiesterase inhibiting activity useful in treating cardiovascular, erectile, and female sexual arousal disorders)
RN 379234-87-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-9-bromo-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L12 ANSWER 15 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:798055 CAPLUS
DOCUMENT NUMBER: 135:339295
TITLE: Daily treatment for erectile dysfunction using a phosphodiesterase 5 (PDE5) inhibitor
INVENTOR(S): Whitaker, John S.; Saenz de Tejada, Inigo; Ferguson, Kenneth M.
PATENT ASSIGNEE(S): Lilly Icos LLC, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001080860	A2	20011101	WO 2001-US12512	20010413
WO 2001080860	A3	20020606		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-558911 A 20000426

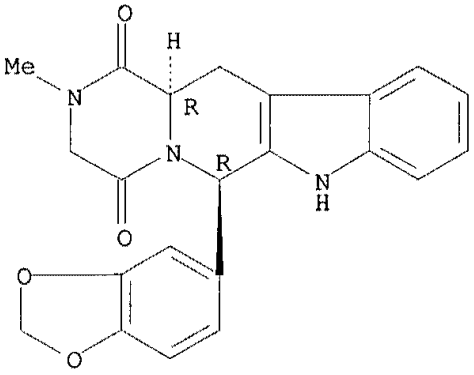
AB The invention relates to phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manuf. In particular, the invention relates to potent inhibitors of cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase type 5 (PDE5) that, when incorporated into a pharmaceutical product at about 1 to about 10 mg unit dosage, are useful for the treatment of sexual dysfunction by daily administration of the PDE5 inhibitor. The articles of manuf. are characterized by PDE5 inhibition, and accordingly provide a benefit in therapeutic areas where inhibition of PDE5 is desired, esp. erectile dysfunction, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes and with an improvement of vascular conditioning.

IT **171596-29-5 171596-40-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(phosphodiesterase 5 inhibitor for daily treatment for sexual dysfunction)

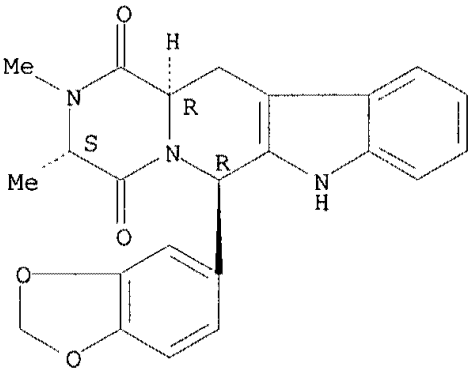
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-40-0 CAPLUS
CN 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-2,3-dimethyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L12 ANSWER 16 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:713326 CAPLUS
DOCUMENT NUMBER: 135:272990
TITLE: Preparation of piperazinylcarbonylaminomethylcarbonylpiperidines as melanocortin-4 receptor agonists
INVENTOR(S): Palucki, Brenda L.; Barakat, Khaled J.; Guo, Liangqin; Lai, Yingjie; Nargund, Ravi P.; Park, Min K.; Pollard, Patrick G.; Sebhat, Iyassu K.; Ye, Zhixiong
PATENT ASSIGNEE(S): Merck + Co., Inc., USA
SOURCE: PCT Int. Appl., 220 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

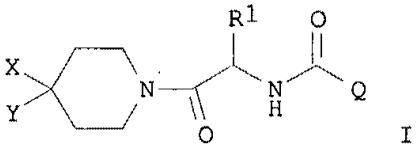
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070708	A1	20010927	WO 2001-US8935	20010320
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 2002019523	A1	20020214	US 2001-812965	20010320

PRIORITY APPLN. INFO.: US 2000-191442P P 20000323
US 2000-242265P P 20001020

OTHER SOURCE(S): MARPAT 135:272990

GI



I

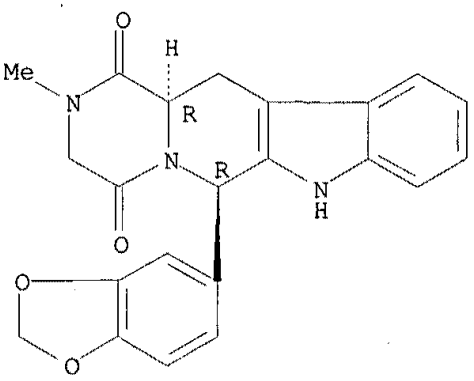
AB Title compds. [I; Q = (substituted) (fused) piperazinyl, morpholinyl, thiomorpholinyl; R1 = H, alkyl, (substituted) cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), etc.; X = (substituted) alkyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), cyano(alkyl), aminosulfonyl(alkyl), etc.; Y = H, alkyl, cycloalkyl(alkyl), (substituted) aryl(alkyl), heterocyclyl(alkyl), heteroaryl(alkyl)], were prepd. as melanocortin-4 receptor (MC-4R) agonists. Thus, capsule formulations contg. title compd. (II) were prepd. Representative I activated MC-4R with IC50<1 .mu.M. I are claimed for the treatment of obesity, diabetes, and sexual dysfunction including erectile dysfunction and female sexual dysfunction.

IT **171596-29-5**, IC-351
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as melanocortin-4 receptor agonists)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 17 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:559496 CAPLUS
DOCUMENT NUMBER: 135:117266
TITLE: Treatment of sexual function disorders with phosphodiesterase 4 inhibitors as monotherapy or in combination with other phosphodiesterase inhibitors or adenylate cyclase activators
PATENT ASSIGNEE(S): Stief, Christian, Germany
SOURCE: Ger. Offen., 4 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

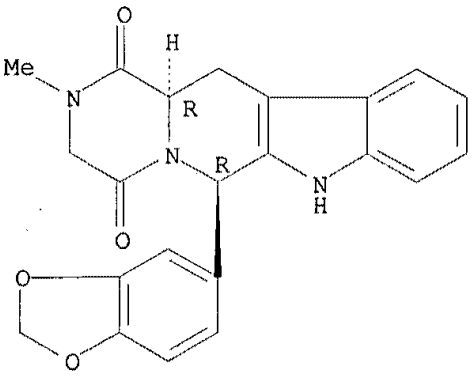
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10004289	A1	20010802	DE 2000-10004289	20000201

AB The invention provides a medicament contg. a phosphodiesterase 4 inhibitor as monotherapy or in combination with other phosphodiesterase inhibitors or adenylate cyclase activators for the treatment of s sexual function disorders.

IT **171596-29-5**, IC 351
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase 4 inhibitors as monotherapy or in combination with other phosphodiesterase inhibitors or adenylate cyclase activators for treatment of sexual function disorders)

RN 171596-29-5 CAPLUS
CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 18 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:541505 CAPLUS
DOCUMENT NUMBER: 135:132460
TITLE: Treatment of sexual function disorders with guanylate cyclase activators, optionally in combination with phosphodiesterase inhibitors
INVENTOR(S): Stief, Christian; Magerl, Hans-Jurgen; Kuthe, Andrea; Uckert, Stefan; Becker, Armin; Farssmann, Wolf Georg; Jones, Udo
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 6 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

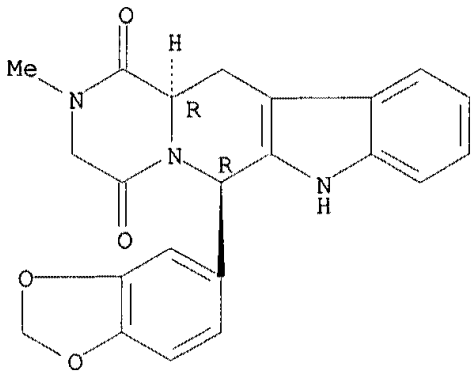
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10002200	A1	20010726	DE 2000-10002200	20000119

AB Medicaments contg. activators of guanylate cyclase and their variants, individually or in combination with phosphodiesterase inhibitors, are provided for the treatment of sexual function disorders. e.g. erectile dysfunction.

IT **171596-29-5**, IC 351
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(guanylate cyclase activators, optionally in combination with phosphodiesterase inhibitors, for treatment of sexual function disorders)

RN 171596-29-5 CAPLUS
CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L12 ANSWER 19 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:338071 CAPLUS
DOCUMENT NUMBER: 134:336223
TITLE: Treatment of pulmonary hypertension with sildenafil or other phosphodiesterase V inhibitor
INVENTOR(S): Butrous, Ghazwan Saleem; Lukas, Timothy; Machin, Ian
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1097711	A2	20010509	EP 2000-309212	20001101
EP 1097711	A3	20010801		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001172182	A2	20010626	JP 2000-335765	20001102

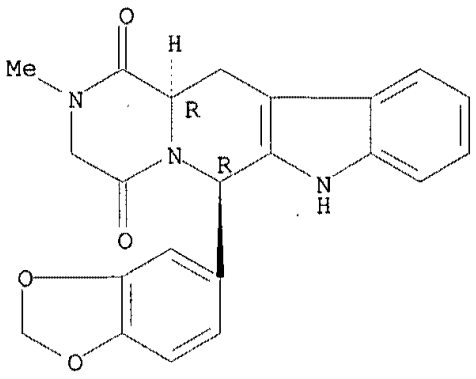
PRIORITY APPLN. INFO.: GB 1999-25970 A 19991102
GB 2000-3235 A 20000211

AB This invention relates to the use of certain cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors, including in particular the compd. sildenafil, for the treatment of pulmonary hypertension.

IT **171596-29-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sildenafil or other phosphodiesterase V inhibitor for treatment of pulmonary hypertension)

RN 171596-29-5 CAPLUS
CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



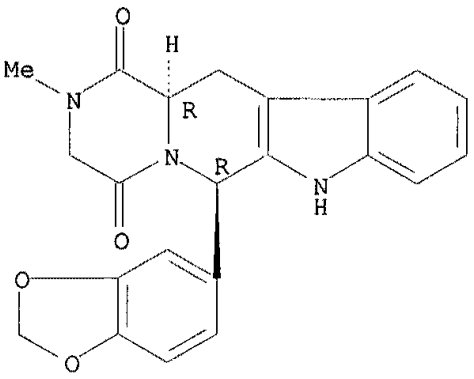
L12 ANSWER 20 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:258390 CAPLUS
DOCUMENT NUMBER: 135:189567
TITLE: IC-351: Treatment of erectile dysfunction treatment of female sexual dysfunction phosphodiesterase 5 inhibitor
AUTHOR(S): Sorbera, L. A.; Martin, L.; Leeson, P. A.; Castaner, J.
CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (2001), 26(1), 15-19
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 20 refs. Significantly more patients (86 %) given IC-351 reported enhanced erections as compared to placebo and a significant change in the patient's median rating was obsd. with IC-351 treatment as compared to placebo. IC-351 (ClalisTM) continues to undergo phase III trials as a treatment for male erectile dysfunction and phase II trials as a treatment for female sexual dysfunction.

IT **171596-29-5**, IC 351
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(IC-351 in treatment of erectile dysfunction and treatment of female sexual dysfunction in humans)

RN 171596-29-5 CAPLUS
CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 21 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:100983 CAPLUS
DOCUMENT NUMBER: 134:152655
TITLE: Pharmaceutical compositions containing .beta.-carboline drugs
INVENTOR(S): Anderson, Neil R.; Hartauer, Kerry J.; Kral, Martha A.; Stephenson, Gregory A.
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008688	A2	20010208	WO 2000-US20981	20000801
WO 2001008688	A3	20010816		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000012901	A	20020416	BR 2000-12901	20000801
EP 1200092	A2	20020502	EP 2000-952371	20000801
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NO 2002000531	A	20020403	NO 2002-531	20020201

PRIORITY APPLN. INFO.: US 1999-147048P P 19990803
WO 2000-US20981 W 20000801

AB Pharmaceutical compns. contg. .beta.-carboline drugs and pharmaceutically acceptable salts and solvates thereof, wherein the drug is in free particulate form, is disclosed. A tablet contained a .beta.-carboline drug 10.00, lactose monohydrate 153.80, spray dried lactose monohydrate 25.00, hydroxypropyl cellulose 4.00, croscarmellose sodium 16.00, hydroxypropyl cellulose 1.75, sodium lauryl sulfate 0.70, microcryst. cellulose 37.50, and magnesium stearate 1.25 mg. The improvement in

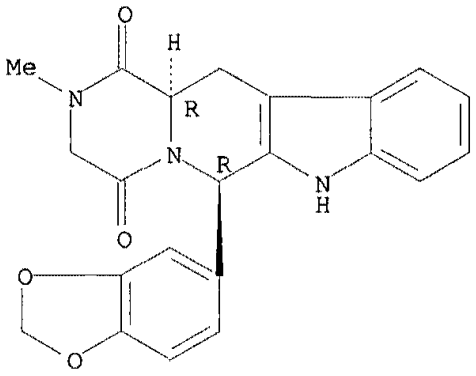
bioavailability of the drug was demonstrated in humans.

IT **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. .beta.-carboline drugs)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L12 ANSWER 22 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:100982 CAPLUS
DOCUMENT NUMBER: 134:152654
TITLE: .beta.-Carboline pharmaceutical compositions
INVENTOR(S): Anderson, Neil R.; Gullapalli, Rampurna P.
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008687	A1	20010208	WO 2000-US11136	20000426
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1200091	A1	20020502	EP 2000-926371	20000426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: US 1999-146924P P 19990803
WO 2000-US11136 W 20000426

AB .beta.-Carboline soft capsules contains a soln. or suspension of a PDE5 inhibitor, and are useful for treating sexual dysfunction. Thus, a formulation contained a .beta.-carboline 25.0, Capmul MCM 177.5, Gelucire 44/14 177.5, and propylene glycol 20.0 mg/capsule. In the phys. study of the above capsule formulation, no sedimentation was obsd. after storage at

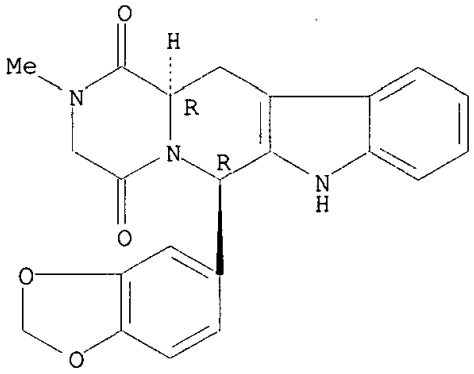
4.degree. for 120 days.

IT **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-carboline pharmaceutical compns.)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 23 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:100981 CAPLUS
DOCUMENT NUMBER: 134:152653
TITLE: .beta.-Carboline pharmaceutical compositions containing cellulose
INVENTOR(S): Oren, Peter L.; Anderson, Neil R.; Kral, Martha A.
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008686	A1	20010208	WO 2000-US11130	20000426
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000012863	A	20020416	BR 2000-12863	20000426
EP 1200090	A1	20020502	EP 2000-926368	20000426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NO 2002000532	A	20020326	NO 2002-532	20020201

PRIORITY APPLN. INFO.: US 1999-146924P P 19990803
WO 2000-US11130 W 20000426

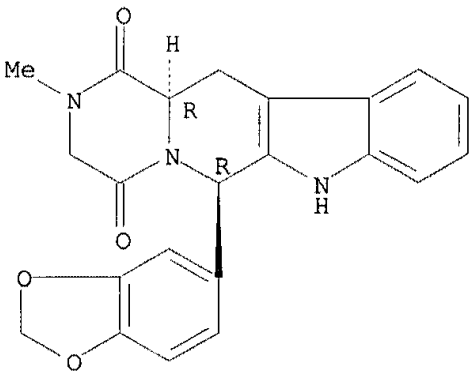
AB .beta.-Carboline formulations contain a c-GMP phosphodiesterase inhibitor, a water-sol. diluent, a lubricant, a hydrophilic binder, a disintegrant, and optional microcryst. cellulose and/or a wetting agent, are useful for treating sexual dysfunction. Thus, a tablet formulation contained a .beta.-carboline 5.00, lactose monohydrate 109.655, lactose monohydrate (spray dried) 17.50, Hydroxypropyl cellulose 4.025, croscarmellose sodium 6.30, SLS 0.49, microcryst. cellulose (granular-102) 26.25, croscarmellose sodium 4.90, and Mg stearate 0.88 mg/tablet.

IT **171596-29-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-carboline pharmaceutical compns. contg. cellulose)

RN 171596-29-5 CAPLUS

CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 24 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:28490 CAPLUS
DOCUMENT NUMBER: 134:95523
TITLE: Drugs for the increase of the cAMP levels
INVENTOR(S): Stief, Christian G.; Ueckert, Stefan; Becker, Armin; Jonas, Udo; Forssmann, Wolf-Georg
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 6 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

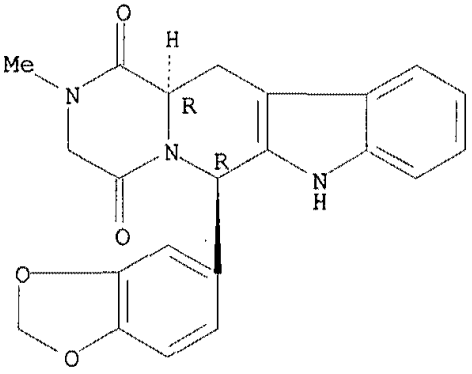
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19931206	A1	20010111	DE 1999-19931206	19990707

AB The invention concerns drugs for the increase of the cAMP levels and/or for the inhibition of the cAMP hydrolysis in smooth muscle tissues and their use for the treatment of diseases. Compds. such as sildenafil increased the cAMP levels in smooth muscle tissues.

IT **171596-29-5**, IC 351
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drugs for increase of cAMP levels)

RN 171596-29-5 CAPLUS
CN 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)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L12 ANSWER 25 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:790302 CAPLUS
DOCUMENT NUMBER: 133:329631
TITLE: Treatment of female arousal disorder with a type V cGMP phosphodiesterase inhibitor
INVENTOR(S): Allemeier, Lora L.; Brashear, Diane L.; Ferguson, Kenneth M.; Pullman, William E.
PATENT ASSIGNEE(S): Lilly Icos LLC, USA
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066114	A1	20001109	WO 2000-US11128	20000426
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1173167	A1	20020123	EP 2000-928382	20000426
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-132129P P 19990430
WO 2000-US11128 W 20000426

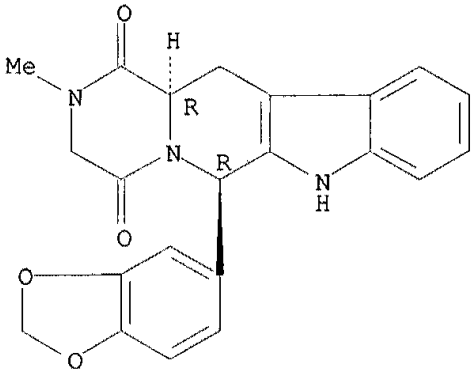
AB A method of treating female arousal disorder in a female patient is disclosed. The method includes orally administering an agent that inhibits cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase type 5 to the female patient.

IT **171596-29-5 171596-40-0 304683-09-8 304683-11-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cGMP phosphodiesterase type V inhibitor for treatment of female arousal disorder)

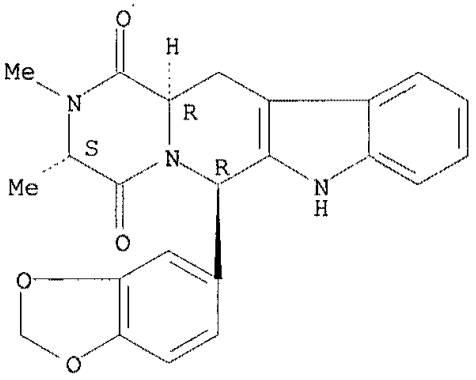
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

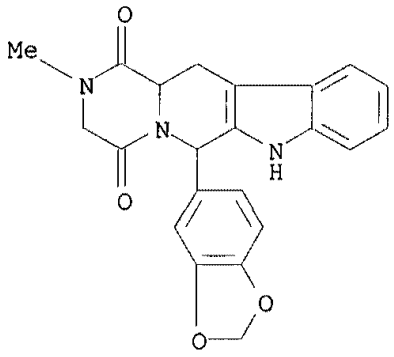


RN 171596-40-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

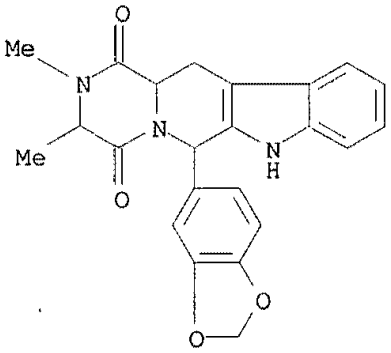
Absolute stereochemistry. Rotation (+).



RN 304683-09-8 CAPLUS
CN 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- (9CI) (CA INDEX NAME)



RN 304683-11-2 CAPLUS
CN 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-2,3-dimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 26 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:785898 CAPLUS
DOCUMENT NUMBER: 133:329627
TITLE: Tetracyclic cGMP-specific phosphodiesterase inhibitors and their use in disease treatment
INVENTOR(S): Daugan, Alain Claude Marie; Gellibert, Francoise
PATENT ASSIGNEE(S): Icos Corp., USA
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US 6143746	A	20001107	US 1998-154051	19980916
WO 9519978	A1	19950727	WO 1995-EP183	19950119

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US

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WO 9703675 A1 19970206 WO 1996-EP3024 19960711
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US 6127542 A 20001003 US 1999-399667 19990921
PRIORITY APPLN. INFO.: GB 1994-1090 A 19940121
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WO 1996-EP3025 A2 19960711
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WO 1999-US19466 W 19990826
OTHER SOURCE(S): MARPAT 133:329627
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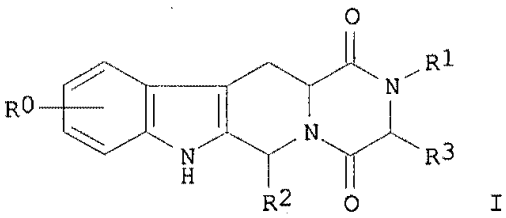

I

AB A compd. of formula I (R0 = H, halogen, C1-6 alkyl; R1 = H, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo-C1-6 alkyl, C3-8 cycloalkyl, C3-8 cycloalkyl-C1-3 alkyl, aryl-C1-3 alkyl, heteroaryl-C1-3 alkyl; R2 = (substituted) monocyclic arom. ring selected from benzene, thiophene, furan, and pyridine, or (substituted) bicyclic ring (a) attached to the rest of the mol. via one of the benzene ring carbon atoms, and wherein the fused ring is a 5- or 6-membered ring which may be satd. or partially or fully unsatd., and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulfur, and nitrogen; R3 = H, C1-3 alkyl, or R1 and R3 together = 3- or 4-membered alkyl or alkenyl chain) and salts and solvates thereof is disclosed. Compd. I is a potent and selective inhibitor of cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase, having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of

cardiovascular disorders and erectile dysfunction. Thus, many I compds. were synthesized and tested in vitro as inhibitors of cGMP phosphodiesterase. 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 showed IC50 of 10 nM.

IT **171488-01-0P 171488-03-2P 171488-04-3P**
171488-06-5P 171488-07-6P 171488-08-7P
171488-09-8P 171488-10-1P 171488-11-2P
171488-12-3P 171488-13-4P 171488-14-5P
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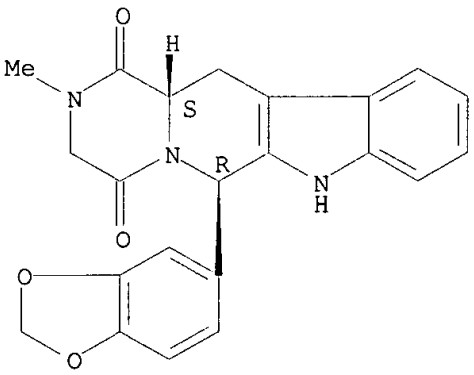
187935-15-5P 303984-32-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tetracyclic cyclic GMP-specific phosphodiesterase inhibitors and their use in disease treatment)

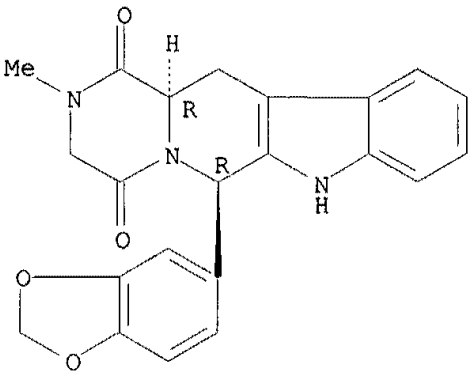
RN 171488-01-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



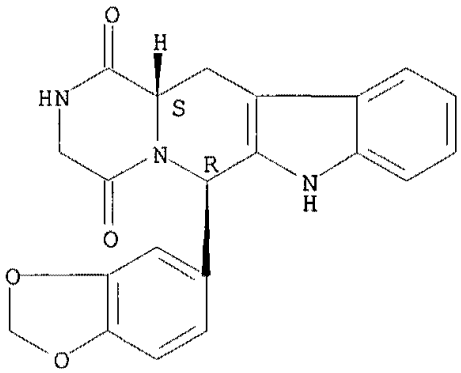
RN 171488-03-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



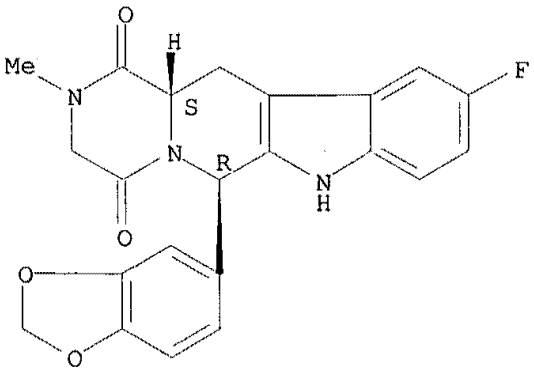
RN 171488-04-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-06-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-10-fluoro-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

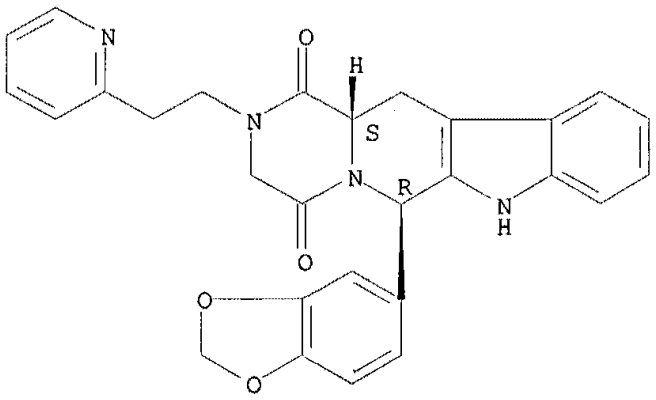
Relative stereochemistry.



RN 171488-07-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-

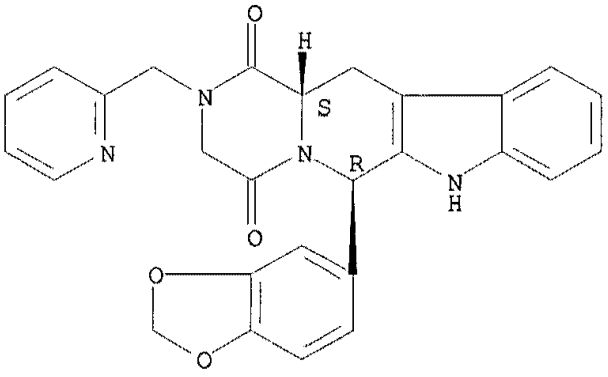
2,3,6,7,12,12a-hexahydro-2-[2-(2-pyridinyl)ethyl]-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



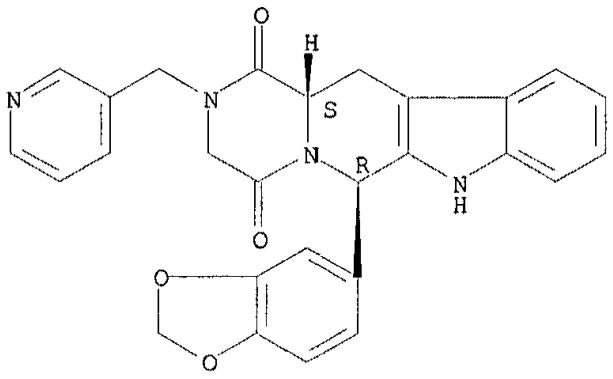
RN 171488-08-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



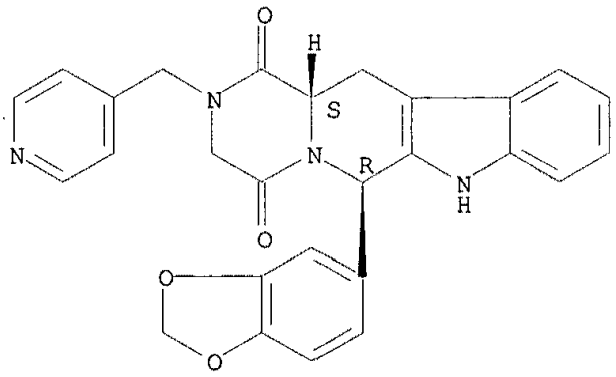
RN 171488-09-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(3-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



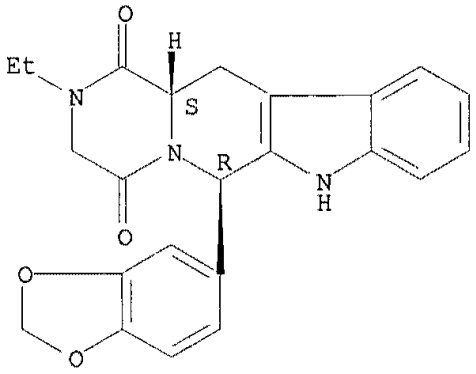
RN 171488-10-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(4-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-11-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-ethyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

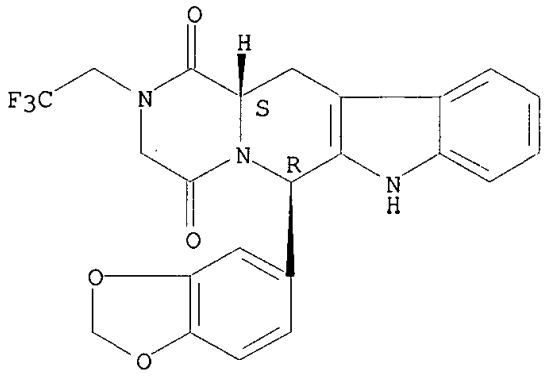
Relative stereochemistry.



RN 171488-12-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-

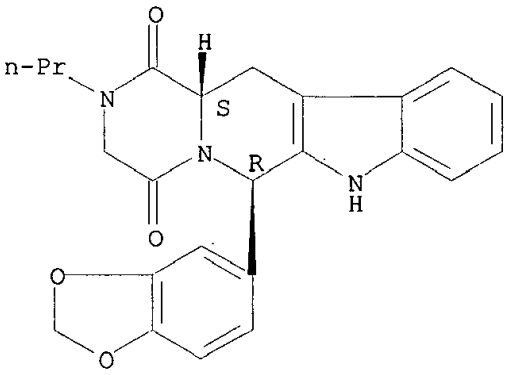
2,3,6,7,12,12a-hexahydro-2-(2,2,2-trifluoroethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



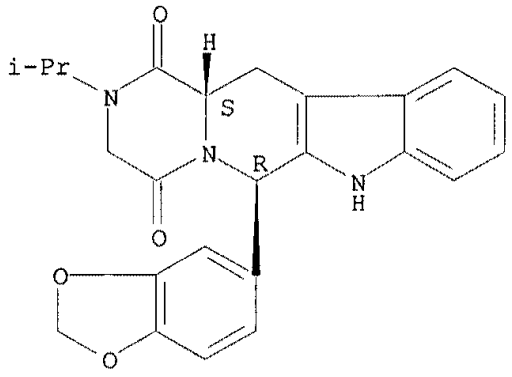
RN 171488-13-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-propyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



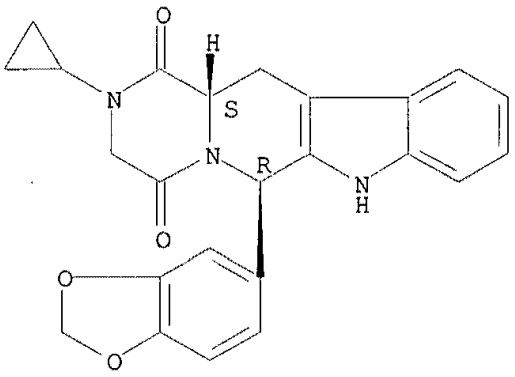
RN 171488-14-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



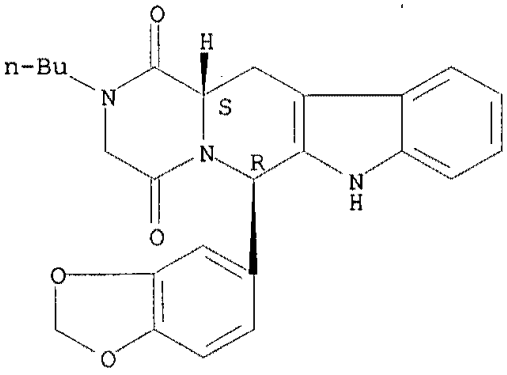
RN 171488-15-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopropyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-16-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

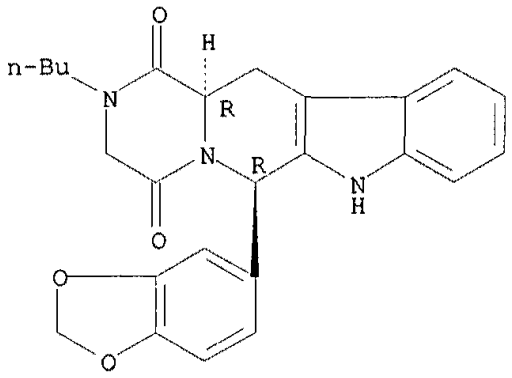
Relative stereochemistry.



RN 171488-17-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-

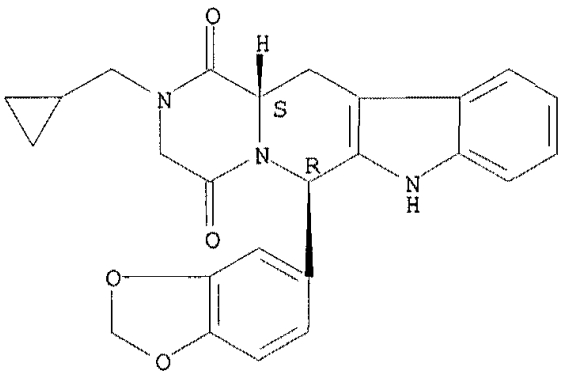
2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-18-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclopropylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-19-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.