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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

531 Rec'd PCT/ 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		
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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	
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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:

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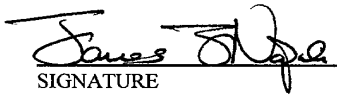
SIGNATURE

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

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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

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 [signature]
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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

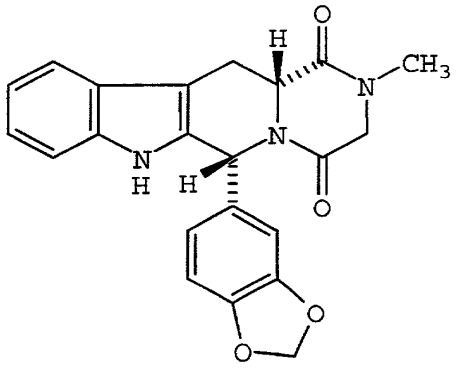
The present invention provides a pharmaceutical dosage form for human pharmaceutical use, comprising about 1 to about 20 mg of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione in a unit dosage form suitable for oral administration.

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

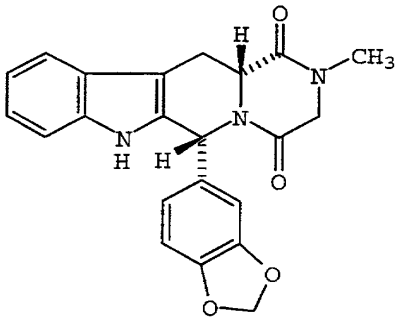
present invention is a solid free of a coprecipitate form of Compound (I), but rather contains solid Compound (I) as a free drug.

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.

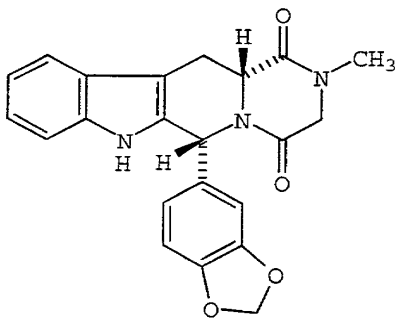
In accordance with the present invention, a unit dose of about 1 to about 20 mg, preferably about 2 to about 20 mg, more preferably about 5 to about 20 mg, and most preferably about 5 to about 15 mg, of Compound (I), administered up to a maximum of 20 mg per 24-hour period, both effectively treats ED 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.

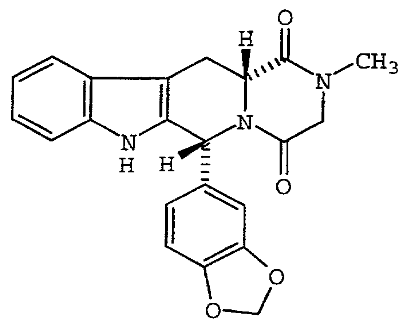
9. The dosage form of claims 1 through 6 for use in treating a condition where inhibition of PDE5 is desirable.

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.

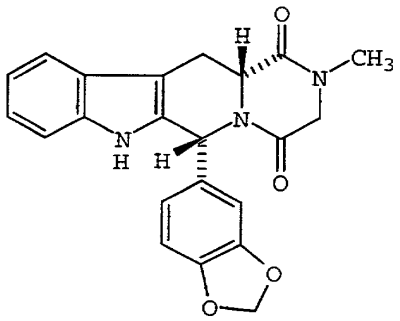
15. The method of claim 13 wherein the unit dose contains about 5 mg of the compound.

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.

PQWER 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.

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.

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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
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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Residence Address - Street 19340 162nd Avenue	Post Office Address - Street 19342 162nd Avenue
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

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

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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	Gupta

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

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	250	8/28/02	H
updated		4/9/03	H
updated		9/16/03	H

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

	Date	Exmr.
Palm Expo Inventor search. ODP	8/28/02	H
STN. Registry, CAPLUS, Embase, WPIDS, Biosis, Medline	7/15/02	H
see search inside		

ISSUE SLIP STAPLE AREA (for additional cross-references)

ISSUING CLASSIFICATION			
ORIGINAL		CROSS REFERENCE(S)	
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)
INTERNATIONAL CLASSIFICATION			
/			
/			
/			
/			
/			^ Continued on Issue Slip Inside File Jacket

INDEX OF CLAIMS

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

Claim Final	Claim Original	Date	Claim Final	Claim Original	Date	Claim Final	Claim Original	Date
	1	8/29/02 7/9/03 9/16/03		51			101	
	2			52			102	
	3			53			103	
	4			54			104	
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	6			56			106	
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	50			100			150	

If more than 150 claims or 9 actions staple additional sheet here

IC10 Rec'd PCT/PTO 19 OCT 2001

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/PTO 19 OCT 2001

U.S. APPLICATION NO. (IF KNOWN, SEE [illegible]) 10/0515[illegible]6	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	$
				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:

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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

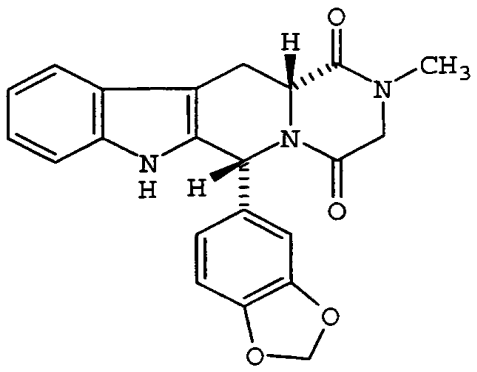
The present invention provides a pharmaceutical dosage form for human pharmaceutical use, comprising about 1 to about 20 mg of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione in a unit dosage form suitable for oral administration.

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

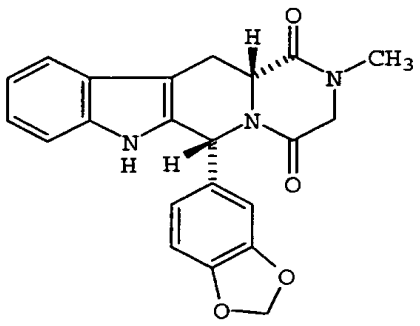
present invention is a solid free of a coprecipitate form of Compound (I), but rather contains solid Compound (I) as a free drug.

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.

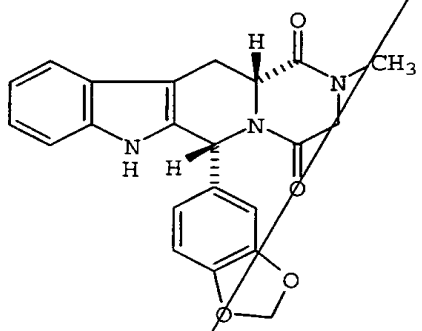
In accordance with the present invention, a unit dose of about 1 to about 20 mg, preferably about 2 to about 20 mg, more preferably about 5 to about 20 mg, and most preferably about 5 to about 15 mg, of Compound (I), administered up to a maximum of 20 mg per 24-hour period, both effectively treats ED 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.

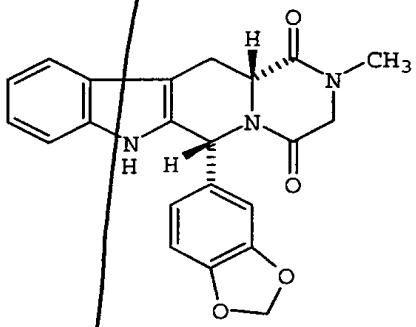
9. The dosage form of claims 1 through 6 for use in treating a condition where inhibition of PDE5 is desirable.

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.

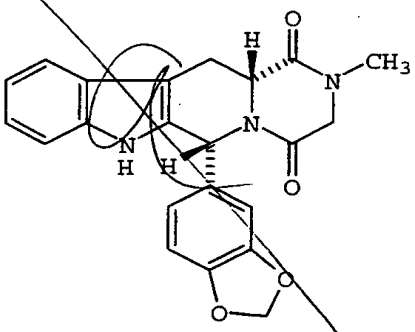
15. The method of claim 13 wherein the unit dose contains about 5 mg of the compound.

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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(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.

Atty. Docket No. 29342/36206A

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:

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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.

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	☒	☐
(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
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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 ☒

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John Steven Whitaker	United States of America
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City (Zip)	City (Zip)
Woodinville (98072) WA.	Woodinville (98072)
State or Country	State or Country
Washington	Washington
Date ☒ 11 Octh 2007	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 ☒

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.

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				☐

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				☐

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				
20						
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48						
49						
50						
TOTAL IND.	1					
TOTAL DEP.	45					
TOTAL CLAIMS	46					

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
53						
54						
55						
56						
57						
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92						
93						
94						
95						
96						
97						
98						
99						
100						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

PTO-875 (12-78)

*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:	"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.

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

Form PCT/IB/331 (July 1992) US0011129

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

Form PCT/IPEA/409 (cover sheet) (January 1994)

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.

Form PCT/ISA/210 (first sheet) (July 1998)

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

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

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
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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.

WO 00/66099 A3

(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.

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

[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

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

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
		CN 1195290 A	07-10-1998
		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
		AT 169018 T	15-08-1998
		AU 689205 B	26-03-1998
		AU 1574895 A	08-08-1995
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		AU 7391298 A	20-08-1998
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		BR 9506559 A	28-10-1997
		CA 2181377 A	27-07-1995
		CN 1143963 A,B	26-02-1997
		CZ 9602116 A	11-06-1997
		DE 69503753 D	03-09-1998
		DE 69503753 T	21-01-1999
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		HR 950023 A	30-04-1998
		HU 74943 A	28-03-1997
		IL 112384 A	16-08-1998
		JP 9508113 T	19-08-1997
		LV 11690 A	20-02-1997
		LV 11690 B	20-06-1997
		NO 963015 A	09-09-1996
		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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		US 6025494 A	15-02-2000
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WO 0020033 A	13-04-2000	JP 2000178204 A	27-06-2000
		JP 2000191518 A	11-07-2000

Form PCT/ISA/210 (patent family annex) (July 1992)

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants:

WILLIAM ERNEST PULLMAN ET AL.

Serial No.: 10/031,556

Filed: October 19, 2001

For: **UNIT DOSAGE FORM**

Attorney Docket No. 29342/36206A

Group Art Unit: Unassigned

Examiner: Unassigned

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on this date:

March 14, 2002

James J. Napoli
Registration No. 32,361
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
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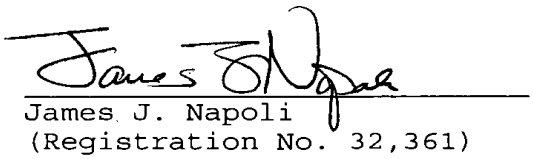
A copy of the International Search Report is enclosed for the convenience of the examiner.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By 

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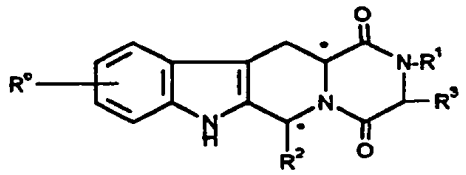
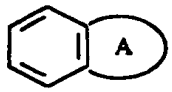


(I)



(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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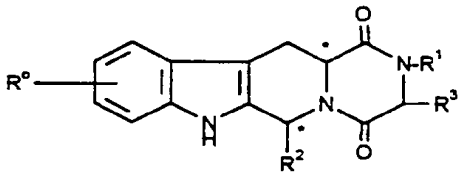
TETRACYCLIC DERIVATIVES, PROCESS OF PREPARATION AND USE

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)

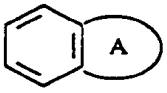


(I)

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

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

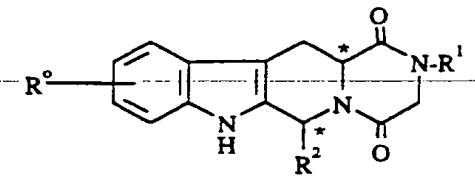
R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl or heteroarylC_{1-3}alkyl;

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)

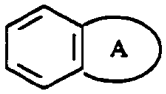


(Ia)

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

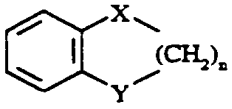
R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring 

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.

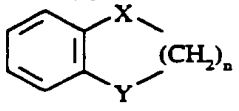
The compounds of formula (I) may contain two or more asymmetric centres and thus can exist as enantiomers or diastereoisomers. In particular, in formula (I) above two ring chiral centres are denoted with asterisks. It is to be understood that the invention includes both mixtures and separate individual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

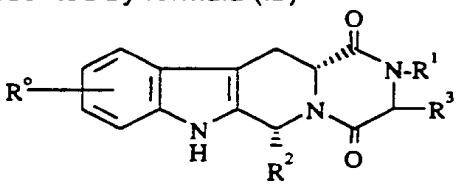
A particular group of compounds of the invention are those compounds of formula (I) in which R^o is hydrogen or halogen (e.g. fluorine), especially hydrogen.

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.

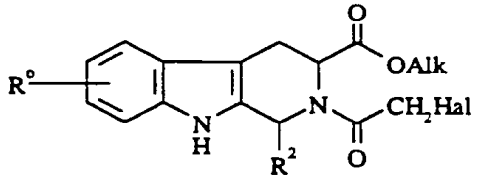
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

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.

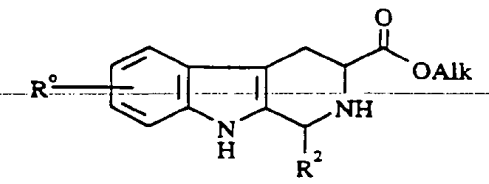
Thus, a process (A) for preparing a compound of formula (I) wherein R^3 represents hydrogen comprises treating a compound of formula (II)



(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)

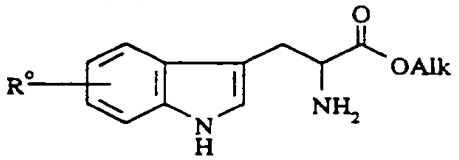
with a haloacetyl halide (e.g. chloroacetyl chloride) in a suitable solvent such as a halogenated hydrocarbon (e.g. trichloromethane or dichloromethane), or an ether (e.g. tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g. a trialkylamine such as triethylamine) or an 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)

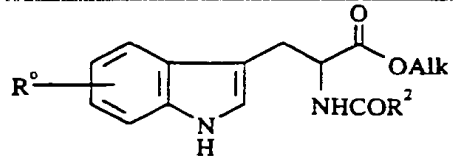
This comprises a Pictet-Spengler cyclisation between a compound of formula (IV) and an aldehyde R^2CHO. The reaction may conveniently be effected in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an aromatic hydrocarbon (e.g. toluene) in the presence of an acid such as 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

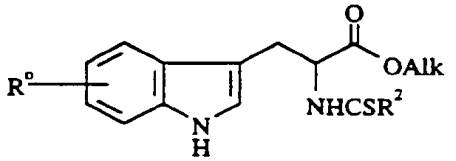
base such as a trialkylamine (for example triethylamine), to provide a compound of formula (V)



(V)

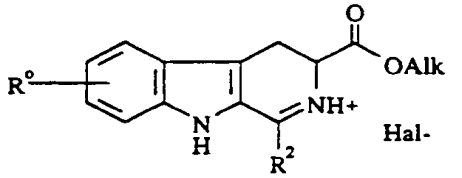
The reaction may be conveniently carried out in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an ether (e.g. tetrahydrofuran) and at a temperature of from -20°C to +40°C.

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)



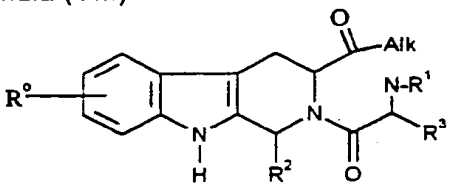
(VII)

(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).

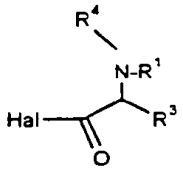
There is further provided by the present invention a process (B) for preparing a compound of formula (I), wherein R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain, which process (B) comprises cyclisation of a compound of formula (VIII)



(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.

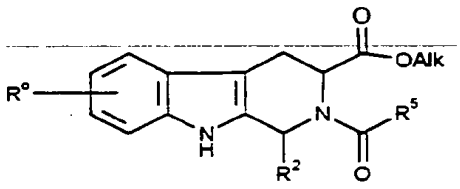
Conveniently a compound of formula (VIII) is prepared by reaction of a compound of formula (III) as hereinbefore described with a compound of formula (IX)



(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 pr paring 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 solv nt 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. After evaporation of THF, the resulting residue 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.

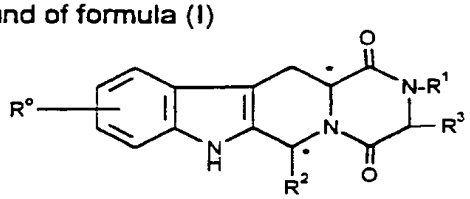
In Vivo Results

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)

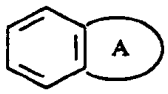


(I)

and salts and solvates thereof, in which:

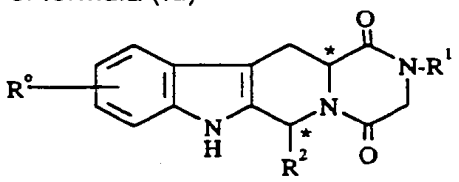
R^o represents hydrogen, halogen or C_{1-6} alkyl;

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)

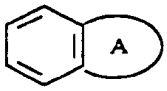


(Ia)

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 

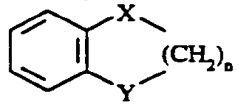
attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen.

3. A compound according to Claim 1 or 2, wherein R° 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.

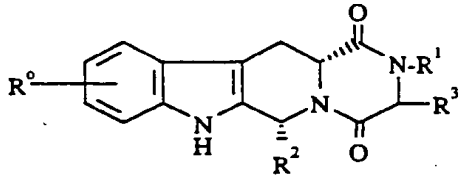
5. A compound according to any of Claims 1 to 3, wherein R^1 and R^3 together represent a 3-membered alkyl chain.

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^0 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.

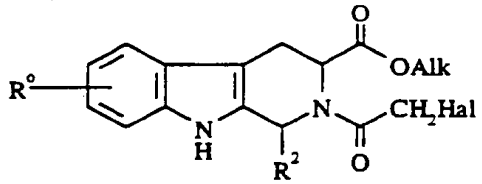
13. A method of treating stable, unstable and variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, vascular disorders, inflammatory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

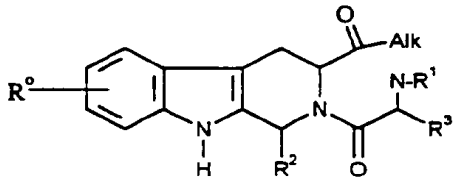
a process (A) for preparing a compound of formula (I), wherein R^3 represents hydrogen which process (A) comprises treating a compound of formula (II)



(II)

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

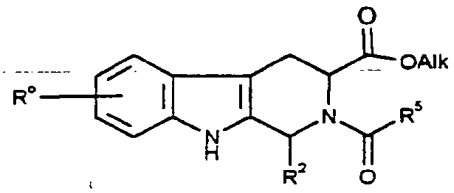
a process (B) for preparing a compound of formula (I), wherein R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain, which process (B) comprises cyclisation of a compound of formula (VIII)



(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)

"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

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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
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	Lauro, P

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INTERNATIONAL SEARCH REPORT

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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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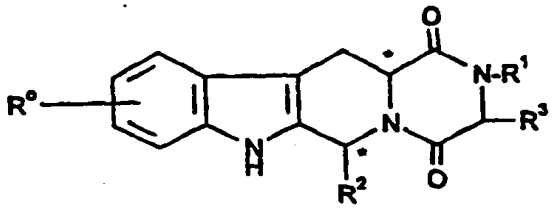
(54) Title: USE OF CGMP-PHOSPHODIESTERASE INHIBITORS TO TREAT IMPOTENCE

(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.

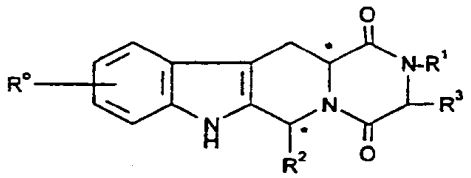
Impotence can be defined as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence 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):

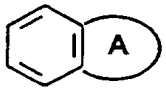


(I)

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.

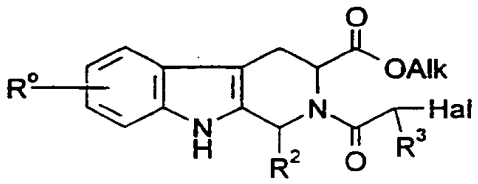
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

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.

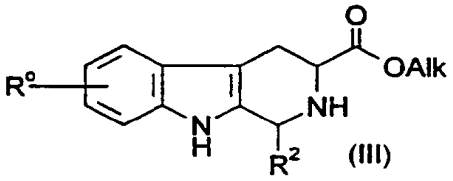
Thus, a process for preparing a compound of formula (I) comprises treating a compound of formula (II)



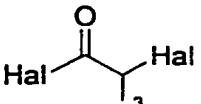
(II)

(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)

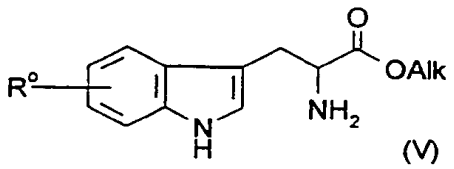
in a suitable solvent such as a halogenated hydrocarbon (e.g. trichloromethane or dichloromethane), or an ether (e.g. tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g. a trialkylamine such as triethylamine) or an alkali metal carbonate or bicarbonate (e.g. $NaHCO_3$). 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 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 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:

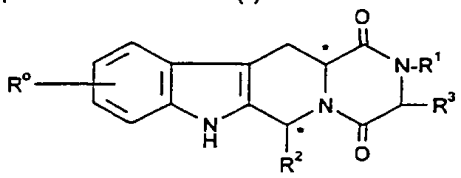
Table 1

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):

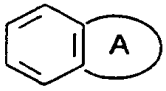


(I)

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.

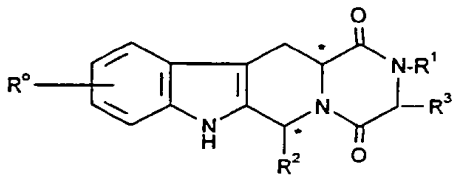
2. Use of a compound selected from

(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):

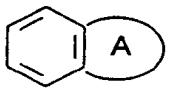


(I)

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.

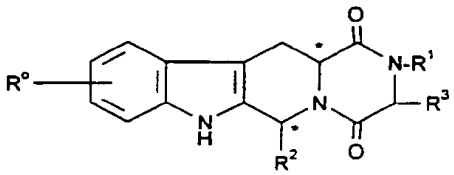
4. Method for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising administration of a compound selected from

(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):

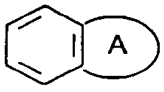


(I)

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

R^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;

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

International 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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"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
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

In ional 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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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US99/07046

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(30) Priority Data:

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09/082,977	21 May 1998 (21.05.98)	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

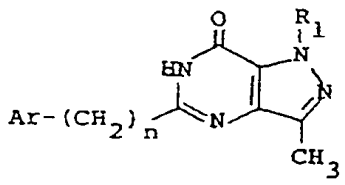
Humans include, of course, males and females. Although the pharmaceutical compositions of the present invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction. Such female sexual dysfunction 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



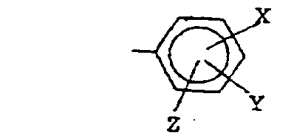
(I)

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;

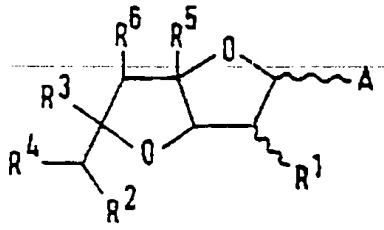
1,3-dimethyl-5-(4-sulfonic acid phenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

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.

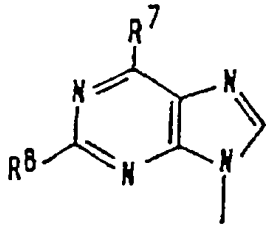
European published application number 0214708, which discloses compounds of the formula

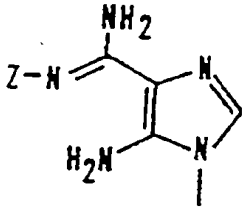


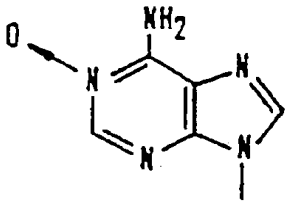
(I)

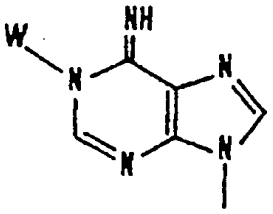
in which:

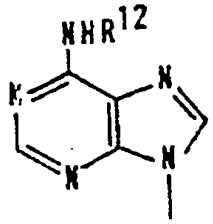
A represents a group of formula:

(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 $-OR^5$;

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^3 represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$, $-NR^{10}R^{11}$ or $-SR^9$;

R^4 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'-methoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-N'-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 N'-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.

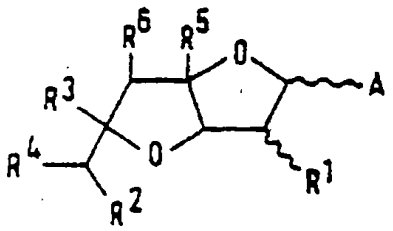
2-Acetylamino-6-desamino-6-hydroxy-4',5'-dihydro-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

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.

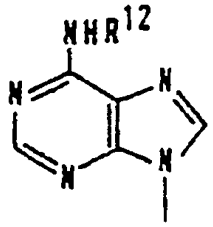
2-Chloro-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

European published application number 0319050, which discloses compounds of the formula



(I)

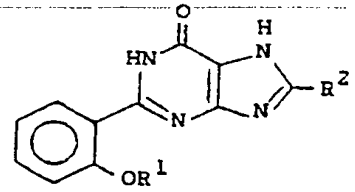
in which:
A represents a group of formula:



;

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



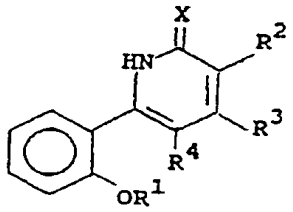
(1)

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



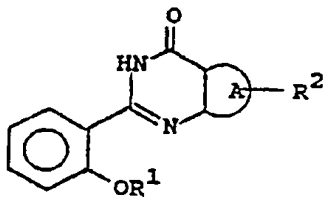
(1)

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-propoxypnenyl)-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.

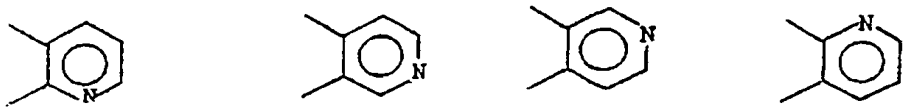
European published application number 0347146, which discloses compounds of the formula



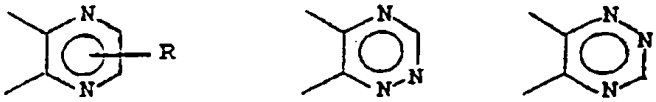
(1)

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)



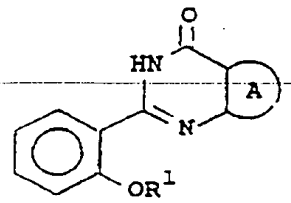
(e) (f) (g),

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-8-(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-8-(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.

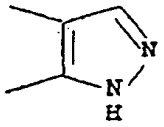
European published application number 0349239, which discloses compounds of the formula



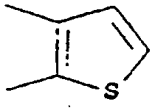
(1)

or a pharmaceutically acceptable salt thereof, wherein

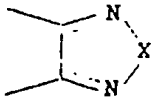
is a ring of sub-formula (a), (b) or (c):



(a)



(b)



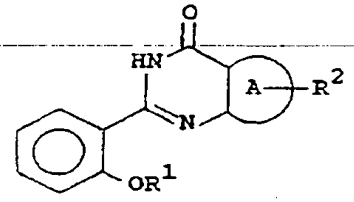
(c),

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 8 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.

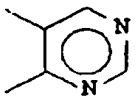
European published application number 0351058, which discloses compounds of the formula



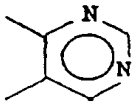
(1)

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)



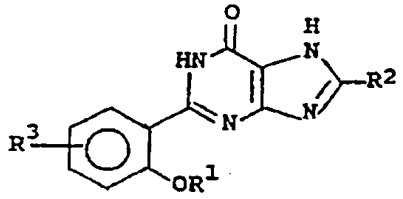
(b).

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



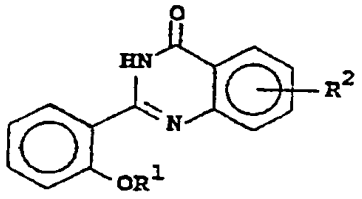
(1)

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-6-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



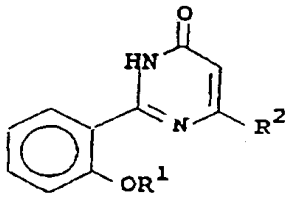
(1)

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



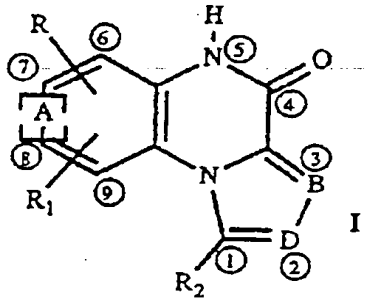
(1)

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:

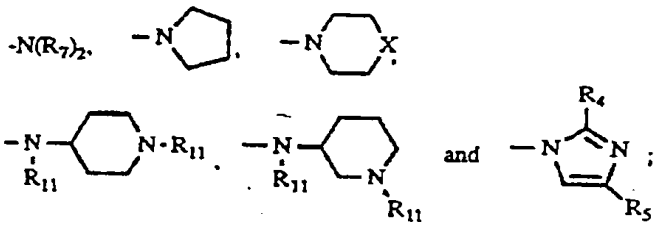
6-amino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-acetamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propionamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-butyramido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-N'-methylureido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4,6-dihydroxy-2-(2-propoxyphenyl)pyrimidine,
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

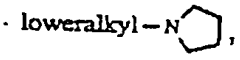


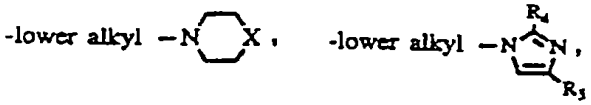
I

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-,

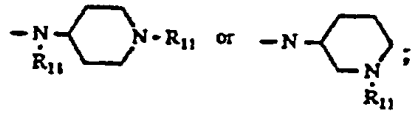


R_2 is hydrogen, lower alkyl, phenyl which may be substituted by up to three methoxy groups, lower alkyl substituted by phenyl which may be substituted by up to three methoxy groups, - lower alkyl $-N(R_8)_2$,

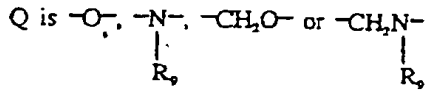


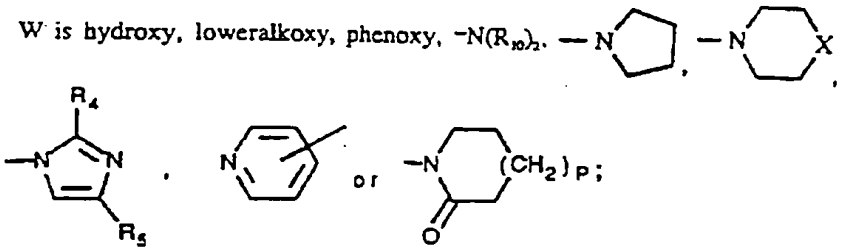


pyridinyl or lower-alkyl pyridinyl;
R_3 is hydrogen, lower alkyl, phenyl, lower alkylphenyl, pyridinyl or loweralkyl pyridinyl;
R_4, R_5 are the same or independently hydrogen or lower alkyl;
R_6 is lower alkyl, phenyl, lower alkylphenyl or pyridinyl;
R_7 are the same or independently hydrogen, loweralkyl, phenyl, pyridinyl,

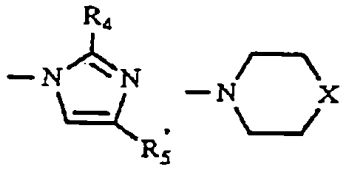


R_8 are the same or independently lower alkyl, phenyl or pyridinyl;

Q is 

W is hydroxy, loweralkoxy, phenoxy, 

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:

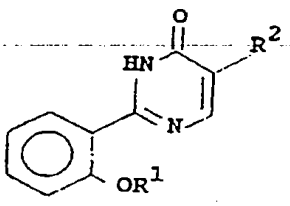
1-ethyl-8-(1H-imidazol-1-yl)-3-methylimidazo[1,5-a]quinoxalin-4-(5H)-one,1-ethyl-8-(1H-imidazol-1-yl)imidazo[1,5-a]quinoxalin-4(5H)-one, 1-ethyl-3-methyl-8-(4-morpholino)-imidazo [1,5-a]quinoxalin-4(5H)-one, 1-ethyl-8-(2-ethyl-4-methyl-1H-imidazol-1-yl)-3-methylimidazo[1,5-a]-quinoxalin-4(5H)-one 1-methyl-8-(2-methyl-1H-imidazol-1-yl)imidazo[1,5a]quinoxalin-4(5H)-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, 8[(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



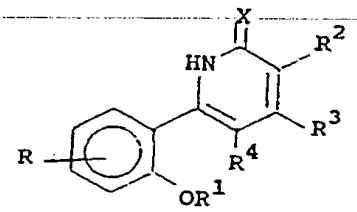
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}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;

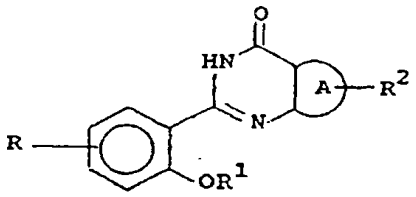
R^2 is hydrogen, -CN, $-CONR^5R^6$, $-CO_2R^7$,5-tetrazolyl, $-NO_2$, $-NH_2$ or $-NHCOR^8$ wherein R^5 to R^8 are independently hydrogen or C_{1-4}alkyl;
R^3 is hydrogen or C_{1-4}alkyl;
R^4 is hydrogen or C_{1-4}alkyl; and
R is halo, C_{1-4}alkyl, C_{1-4}alkoxy, cyano, $-CONR^9R^{10}$, $-CO_2R^{11}$, $-S(O)_nC_{1-4}$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-propoxyphonyl)-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)

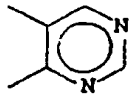
or a pharmaceutically acceptable salt thereof, wherein

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 ;

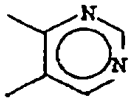
R^2 is C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, -NHCOR^3 wherein R^3 is hydrogen or C_{1-6} alkyl, or -NR^4R^5, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring, or R^4 and R^5 are independently hydrogen, C_{3-5}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) :

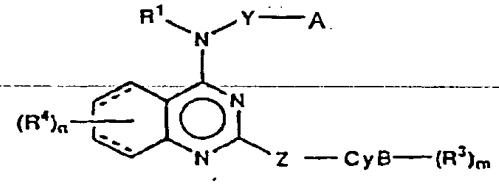


(a)



(b).

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_{1-5} alkylene;
A is
(i) -CyA-$(R^2)_1$,
(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-$(R^2)_1$;
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-$(R^2)_1$ 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:

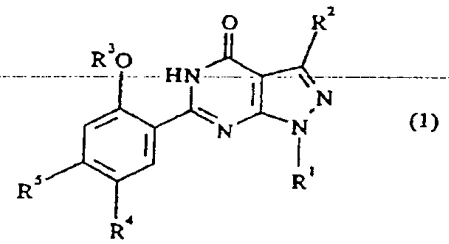
4-phenylmethylamino-2-(3-pyridyl)quinazoline,
4-(3-methylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3,4-dimethoxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-carboxyphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(3-methoxycarbonylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,
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-G-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-azepinyt)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-methytthio-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



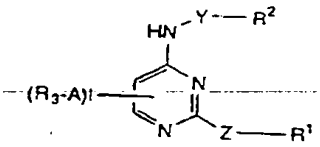
(1)

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;

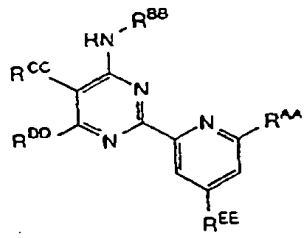
R3 is (i) 4-15 membered heterocyclic ring containing one or two hetero atoms chosen from nitrogen, oxygen and sulphur, not more than one hetero atom being oxgen or sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro, cyano, ethynyl and groups of formula:

-SONR7R8

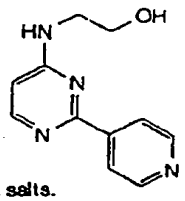
wherein R7 and R8 are independently hydrogen or C1-4 alkyl.
(ii) C4-15 carbocyclic ring,
(iii) a group of formula:

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:



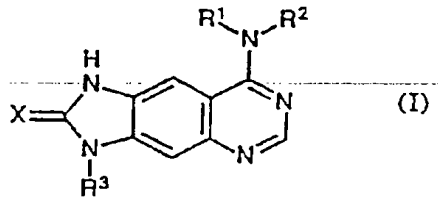
and its pharmaceutically acceptable salts.

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

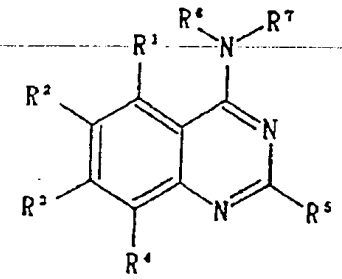
European published application number 0668280, which discloses compounds of the formula



(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

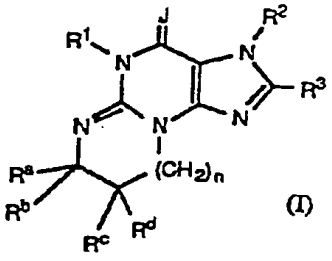


(I)

(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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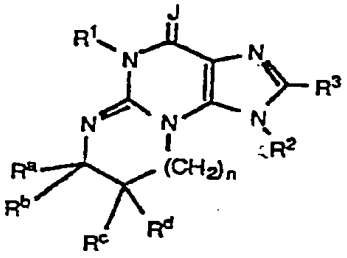
and



(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;

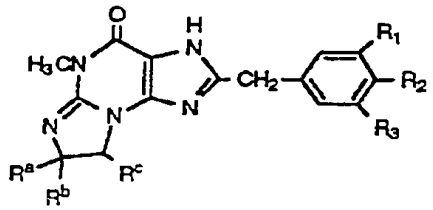
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(cyclohexylmethyl)-

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;

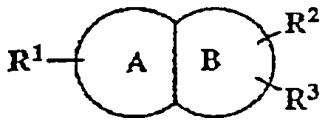
(+)-2-benzyl-7, 8-dihydro-5-methyl-7-(1-methylethyl)-1H-imidazo[2,1-b]-purin-4(5H)-one;

(+,-)-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;

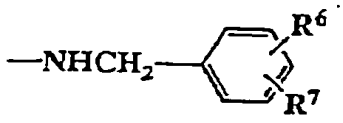
R^1 represents a group represented by the formula: $-NR^4R^5$ (wherein R^4 and R^5 may be the same or different

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:

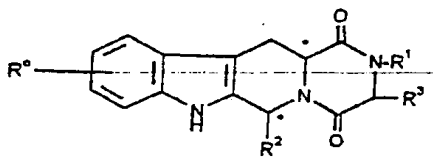
(wherein R^8 represents a carboxyl or tetrazolyl group which may be protected),
or a halogen atom;
and

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

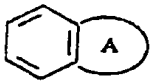


(I)

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

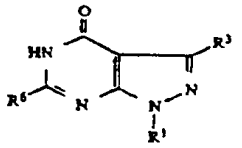
R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

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:

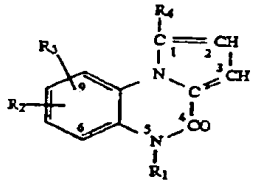
R^1 is hydrogen, alkyl, C_4 to C_7 cycloalkyl, C_4 to C_7 cycloalkyl substituted by C_1 to C_{10} alkyl or hydroxyl, 2- or 3-tetrahydrofuranyl, 3-tetrahydrothienyl 1,1, -dioxide, C_4 to C_7 cycloalkyl-C_1 to C_{10} alkyl, carboxy-C_1 to C_{10} alkyl, carbo-C_1 to C_4 lower-alkoxy-C_1 to C_{10} alkyl, 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

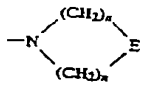
where Alk is C_1–C_6-alkyl, C_2–C_6-hydroxyalkyl or C_3–C_6-cycloalkyl and the symbol A represents:

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

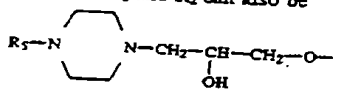
where D is phenyl, C_1–C_6-alkyl, C_3–C_7-cycloalkyl, hydroxy, C_1–C_6-alkoxy, C_3–C_7-cycloalkyloxy, morpholino, pyrrolidino, piperidino, homopiperidino, piperazino, —NHR_5 or —NR_5R_6 and R_5 and R_6 have the meanings given hereinabove;

4) The group:

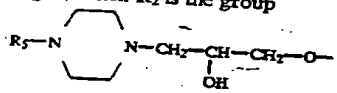


where n can be the integers 1-3 and E represents CH_2, oxygen, sulfur, NH, CHOH, CH—C_1–C_6-alkyloxy, CH—C_2–C_6-alkanoyloxy, CHC_6H_5, CHCOD, CH—$CH_2C_6H_5$, N—C_1–C_6-alkyl, N—C_1–C_6-hydroxyalkyl, N—C_6H_5, N—$CH_2C_6H_5$, N—$CH(C_6H_5)_2$, N—$(CH_2)_2$—OH, N—$(CH_2)_3$—OH or NCOD and the phenyl 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

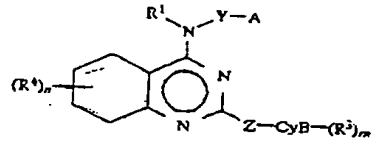


R_4: hydrogen or halogen, where R_1 can also be hydrogen, when R_2 is the group



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,

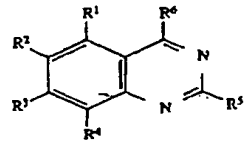
4-(3-trifluoromethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,

4-(2-phenoxyethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline or

4-(2-phenoxycthyl)amino-2-(1-imidazolyl)quinazoline,

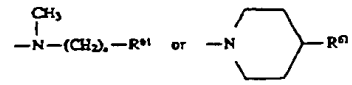
and pharmaceutically acceptable acid addition salts

U.S. Patent No. 5,576,322 discloses compounds of the formula

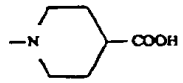


(I)

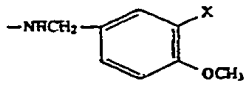
wherein R1, R3, and R4, each of which may be the same or different from each other, may each represent a hydrogen atom, a halogen atom or a lower alkyl group or a lower alkoxy hydrogen atom, R2 is a halogen or cyan group R5 is a group represented by the formula:



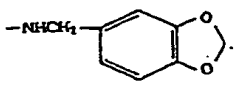
wherein u is 3 or 4 and R61 represents a carboxyl group which may be protected or a heteroaryl group; or R5 is a group represented by the formula:



and R6 is a group represented by the formula



wherein X is hydrogen atom or a halogen atom or



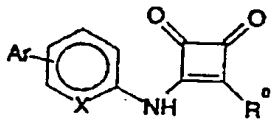
or the pharmacologically acceptable salt thereof

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,

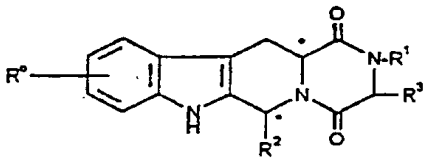
3-amino-4-[3-(2-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

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

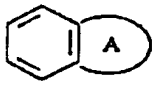


(I)

and salts and solvates thereof, in which:

R^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;

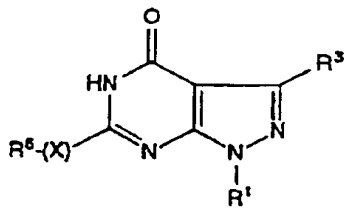
R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected fr m oxygen, sulphur and nitrog n; 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:

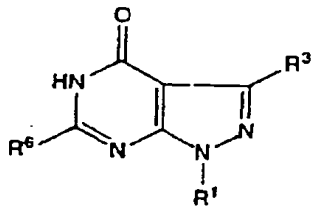
1-cyclopentyl-3-ethyl-6-(4-methoxyphenylmethyl)pyrazolo [3,4-d]pyrimindin-4-one,

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,

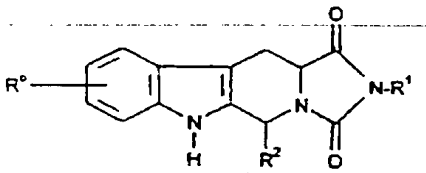
1-cyclopentyl-3-ethyl-6-[4-(1-imidazolyl)phenyl]pyrazolo [3,4-d]pyrimindin-4-one,

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

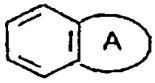
(e) a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from oxygen, nitrogen and sulphur, and being optionally substituted by one or more C_{1-6}alkyl, and optionally linked to the nitrogen atom to which R^1 is attached via C_{1-6}alkyl;

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:

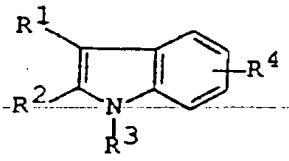
Cis-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-5-(4-methoxyphenyl)-2-methyl-5,6,11,11a-tetrahydro-1H-imidazo [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

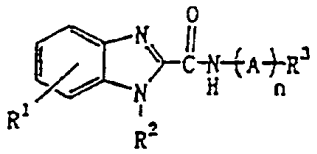
optionally substituted with protected carboxy, carboxy or acyl;

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 pyridylcarbonyl 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.

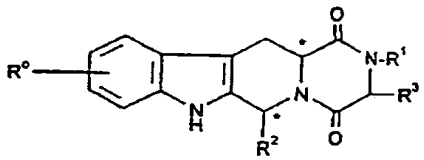
1-Benzyl-6-chloro-2-{1-[3-(1,2,4-triazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.

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;

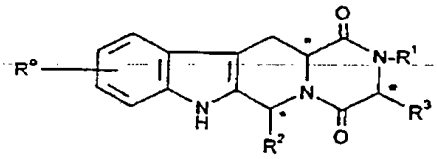
for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

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



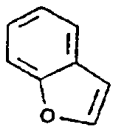
(I)

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

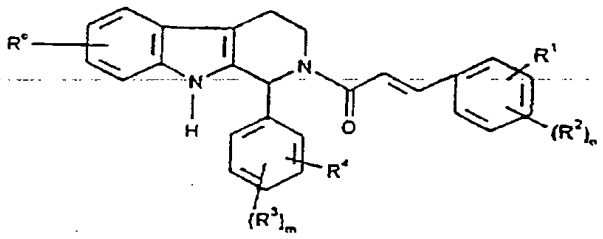
R^3 represents hydrogen or C_{1-3}alkyl.

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,

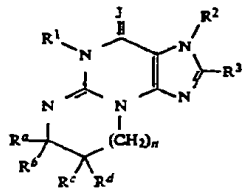
-O-C_{1-4}alkylene -C(=0)OR^a,
-C_{1-4}alkylene-O-C_{1-4}alkylene-C(=0)OR^a,
-C(=0)$NR^aSO_2R^c$,
-C(=0)C_{1-4}alkylene Het, wherein Het represents 5- or 6-membered heterocyclic group as defined above,
-C_{1-4}alkylene NR^aR^b,
-C_{2-6}alkenyleneNR$^aR^b$,
-C(=0)NR^aR^b,
-C(=0)NR^aR^c,
-C(=0)NR^aC_{1-4}alkyl 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 repres nts 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



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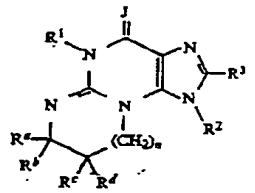
or



(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 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)-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-

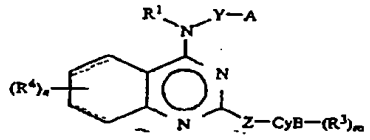
carboxylic acid, methyl ester;
cis-5,6a,7,8,9,9a-Hexahydro-2-bromo-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(methylaminosulfonyl)-5-methyl-3-(phenylmethyl)cyclopent[4,-5]imidazo[2,1-b]purin-4(3H)one;
cis-1-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-b]purin-4-(1H)one;

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-(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); 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;

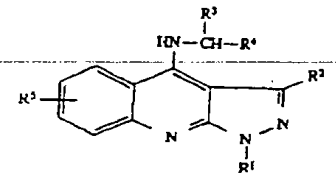
or pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

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,

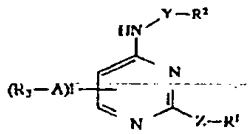
1-ethyl -6-nitro-N-[cyclohexylmethyl]- 1H-pyrazolo [3,4-b]quinolin-4-amine,

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:

—$SO_2NR^7R^8$

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,

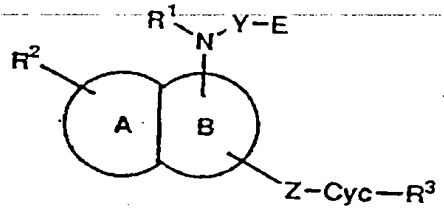
or pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable salts thereof.

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,

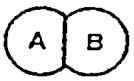
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-methoxyphenyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-furyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-thienyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-pyridyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-methoxyethyl)aminopyrimidine,
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 paten t application No. 0728759 discloses compounds of the formula

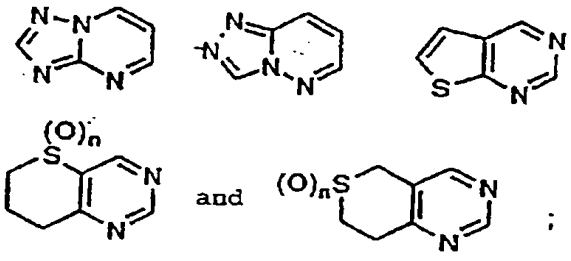


(I)

wherein



is a heterocycle selected from



;

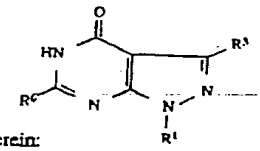
n is 0, 1 or 2;
Y is single bond or C1-6 alkylene;
Z is single bond, C1-2 alkylene or vinylene;
E is

(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,

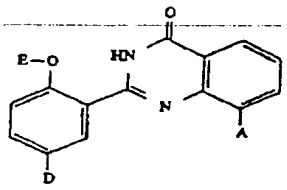
1-Cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

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,

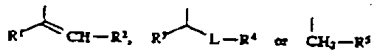
U.S. Patent No. 5,721,238 discloses compounds of the formula



(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,

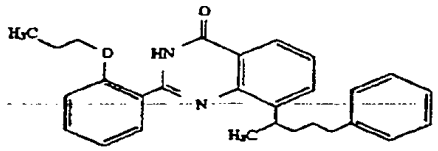
D represents hydrogen, or represents a group of the formula $-SO_2-NR^8R^9$,

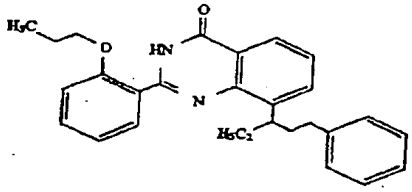
wherein

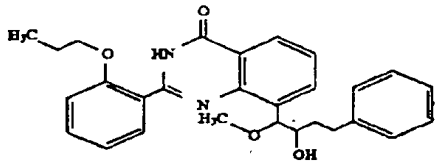
R^8 and R^9 are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, or, together with the nitrogen atom, form a 5- to 6-membered saturated heterocyclic radical which has up to 2 further hetero 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

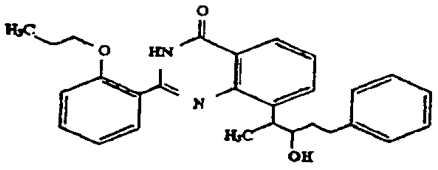
E represents straight-chain or branched alkyl having up to 8 carbon atoms, and tautomers and salts thereof.

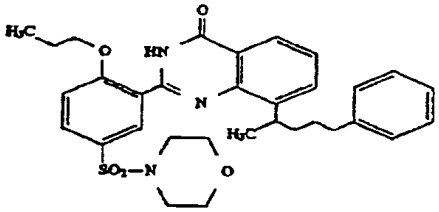
Preferred compounds include:

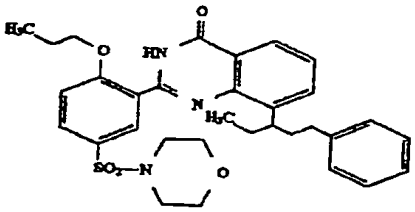




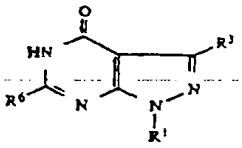








U.S. Patent No. 5,294,612 discloses compounds of the formula



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;

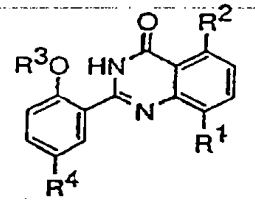
R^3 is, C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl, lower-alkoxyphenyl-C_1 to C_4 lower-alkyl, diC_1 to C_4 lower-alkoxy-phenyl-C_1 to C_4 lower-alkyl, pyridyl-C_1 to C_4 lower-alkyl, C_4 to C_7 cycloalkyl-C_1 to C_4 lower-alkyl, phenylamino, diC_1 to C_{10} alkylamino, halogen, trifluoromethyl, 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;

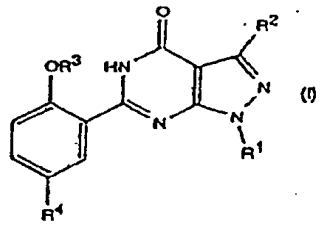
8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one;

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_4 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;

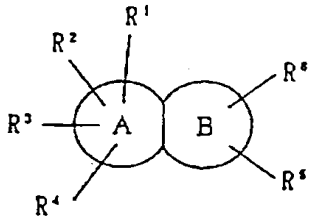
6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

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

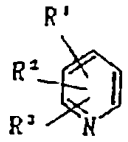


(1)

[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.

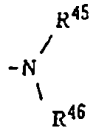
Provided that the ring A and the ring B are combined sharing two atoms and the atoms shared may be either a carbon atom or a nitrogen atom.

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

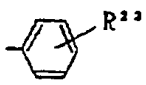
(wherein R^7 represents a lower alkyl group, and n represents 0 or an integer of 1 to 2), or a group represented by the formula



(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

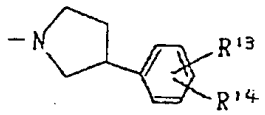
(wherein R^8 represents a lower alkyl group, and m represents 0 or an integer of 1 to 2), a group represented by the formula $-O-R^9$ (wherein R^9 represents a hydroxyalkyl group which may be protected, a carboxyalkyl group which may be protected or a benzyl group which may be substituted), a group represented by the formula



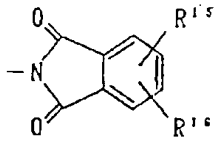
(wherein R^{23} represents a hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group or a hydroxyalkyloxy group), a heteroaryl group which may be substituted, a 1,3-benzdioxolyl group which may be substituted, a 1,4-benzdioxyl group which may be substituted, a 1,3-benzdioxolylalkyl 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).

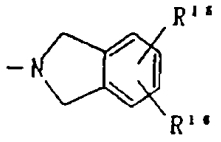
R^6 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a lower alkyl group, a lower alkoxy group, a lower alkenyl group, a 1,3-benzdioxolylalkyloxy group, a 1,4-benzdioxylalkyloxy group, a phenylalkyloxy group which may be substituted, a group represented by the formula



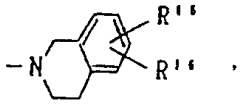
(wherein R^{13} and R^{14}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{13} and R^{14} may together form methylenedioxy or ethylenedioxy), a group represented by the formula



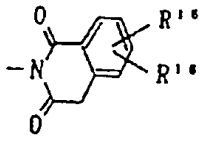
a group represented by the formula



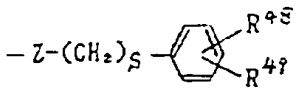
a group represented by the formula



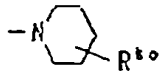
a group represented by the formula



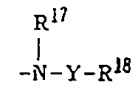
(in these formulas, R^{15} and R^{16}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{15} and R^{16} may together form methylenedioxy or ethylenedioxy), a piperidine-4-spiro-2'-dioxan-1-yl group, 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

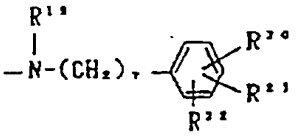


(wherein R^{50} represents a hydroxyl group, a halogen atom, a lower alkyl group, a lower alkoxy group, a carboxyl group which may be protected, a cyano group, a hydroxyalkyl group or a carboxyalkyl group), a group represented by the formula



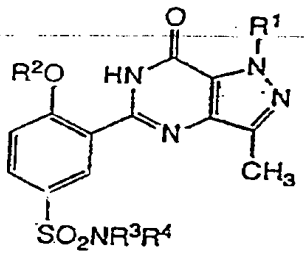
[wherein R^{17} represents a hydrogen atom, a lower alkyl group, an acyl group, a lower alkoxyalkyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; Y represents a group represented by the formula $-(CH_2)_q-$ (wherein q is 0 or an integer of 1 to 8), or a group represented 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_3–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;

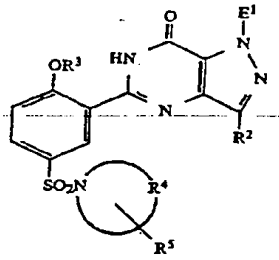
1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

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;

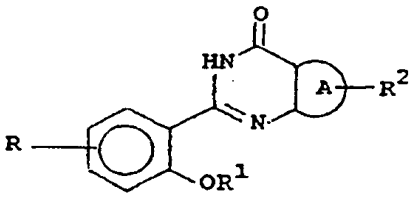
R^3 is C_1–C_6 alkyl, C_3–C_6 alkenyl, C_3–C_6 alkynyl, C_3–C_7 cycloalkyl, C_1–C_6 perfluoroalkyl or (C_3–C_6 cycloalkyl)C_1–C_6 alkyl;

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

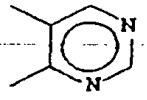
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkyl C_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups ;

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

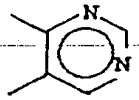
n is 0, 1 or 2, -OR^6, -CO_2R^7 or -NR^8R^9 wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -$S(O)_nC_{1-6}$alkyl, -OR^6 or -NR^8R^9 groups ;

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)

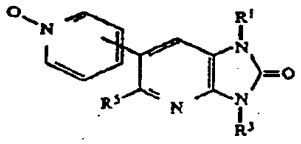


(b).

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

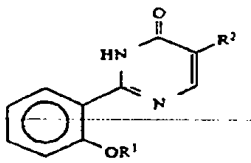


wherein
R_1 and R_3 are hydrogen or lower-alkyl;
R_5 is lower-alkyl or fluorinated lower-alkyl; and the pyridine-N-oxide is attached at the 4- or 3-position; or a pharmaceutically acceptable acid-addition salt thereof.

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



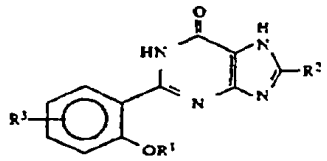
(I)

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



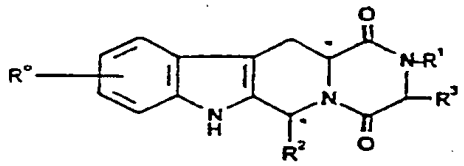
(I)

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:

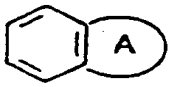


(I)

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

R^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.

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

Inter ional Application No
PC I/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 an 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

Inter onal Application No
PCT/US 99/07046

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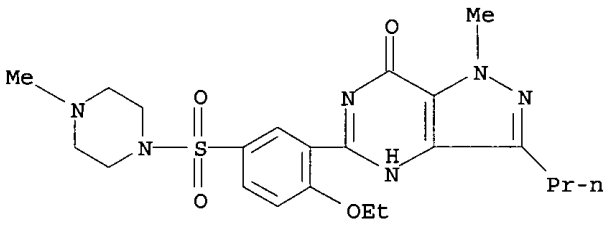

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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

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  Please note that search-term pricing does apply when
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Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
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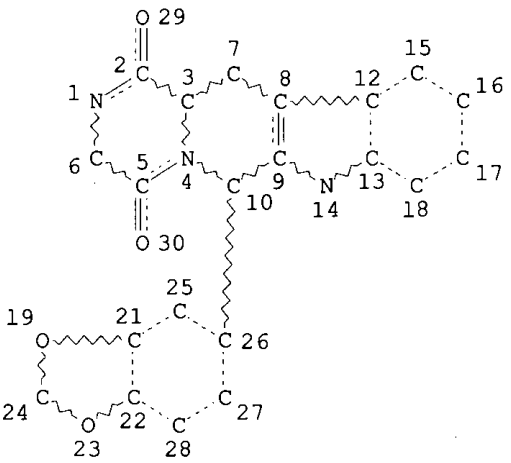

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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  28

STEREO ATTRIBUTES: NONE
L10          178 SEA FILE=REGISTRY SSS FUL L8

100.0% PROCESSED    189 ITERATIONS                    178 ANSWERS
SEARCH TIME: 00.00.01


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FILE 'CAPLUS' ENTERED AT 14:30:16 ON 16 JUL 2002
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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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L8              STR
L10         178 SEA FILE=REGISTRY SSS FUL L8
L11          38 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10
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L8              STR
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
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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

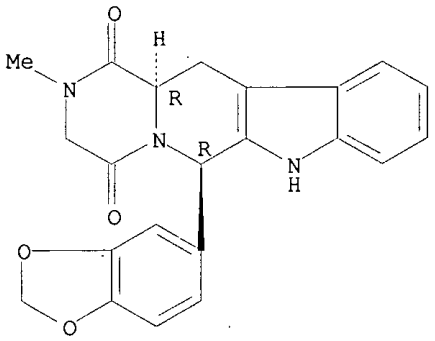
AB Animal cells and animals carrying a knockout of the gene for the cyclic nucleotide phosphodiesterase PDE11 are described for use in anal. of the role of the enzyme, esp. in spermatogenesis and in the screening of drugs for regulation of spermatogenesis. Heterozygous knockout mice show lowered levels 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

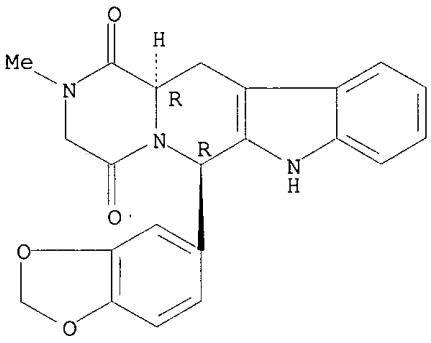
AB The invention relates to the use of cGMP phosphodiesterase V inhibitors, including in particular the compd. sildenafil, for the treatment of premature ejaculation in patients with normal erectile function.

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:

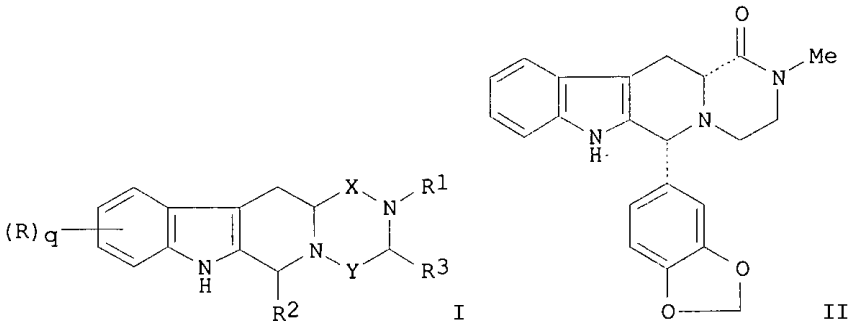
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036593	A1	20020510	WO 2001-US31364	20011009

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



I II

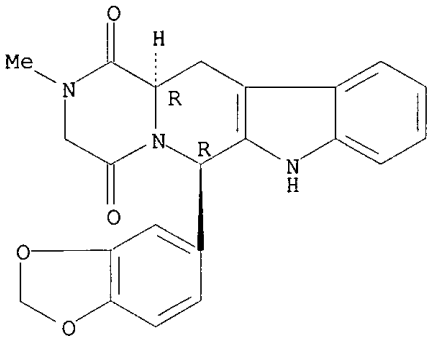
AB 2,3,6,7,12,12A-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole derivs., such as I [R = halo, alkyl; R1 = H, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heteroarylalkyl, etc.; R2 = monocyclic arom. ring, such as benzene, thiophene, furan, pyridine, etc.; R3 = H, alkyl; R1,R3 = fused carbocyclic 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

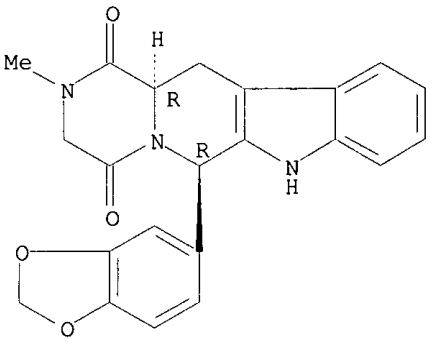
PRIORITY APPLN. INFO.: US 1997-958816 B2 19971028
US 1998-181070 A2 19981027
US 1999-467094 A2 19991210

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

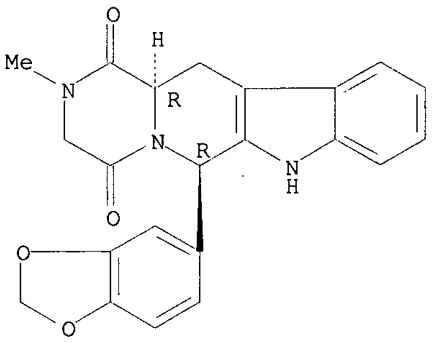
resistance syndrome.

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

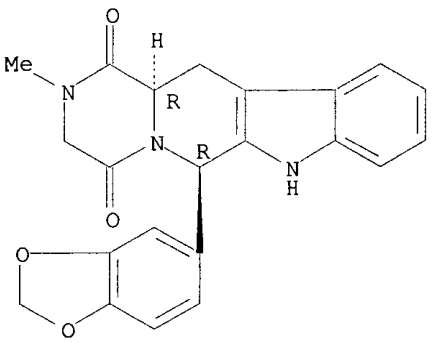
phosphodiesterases.

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
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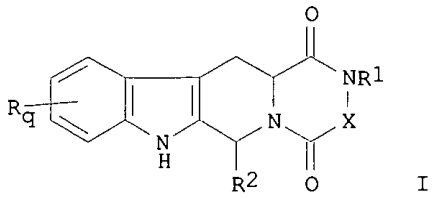

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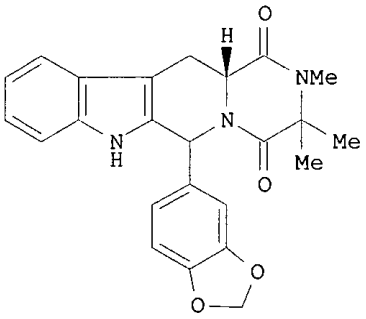


II

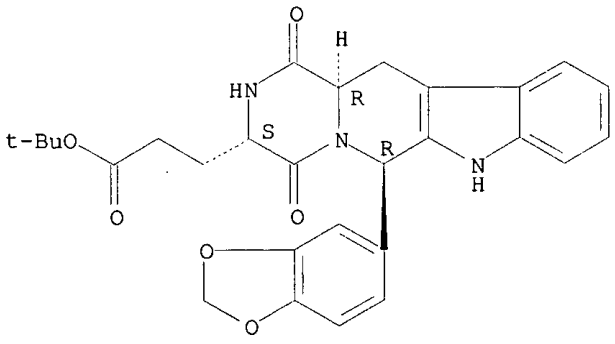
AB Compds. I [R = halo, alkyl; q = 0-4; R1 = H, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl; R2 is an optionally substituted monocyclic arom. ring selected from benzene, thiophene, furan, and pyridine or an optionally substituted bicyclic ring; X = NH or 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

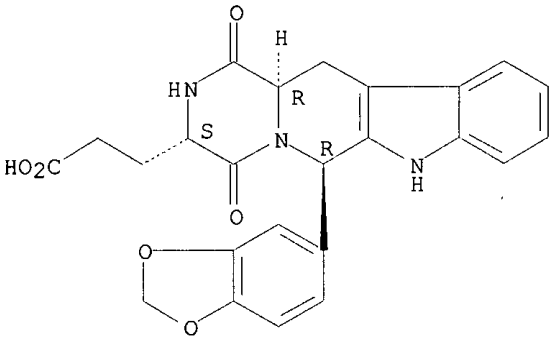
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propanoic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 1,1-dimethylethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

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)

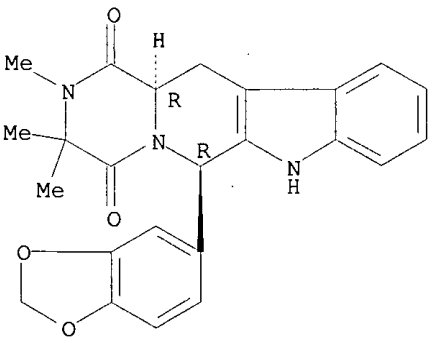
Absolute stereochemistry. Rotation (+).



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)

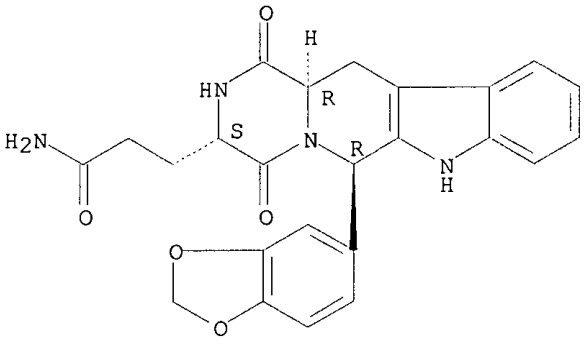
Absolute stereochemistry.



RN 395665-36-8 CAPLUS

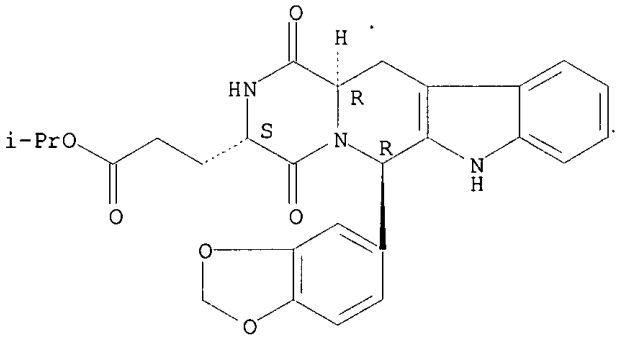
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propanamide, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



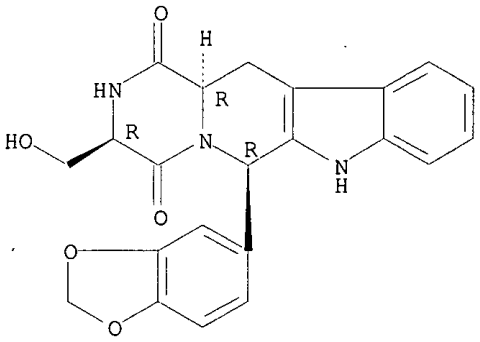
RN 395665-41-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propanoic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 1-methylethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



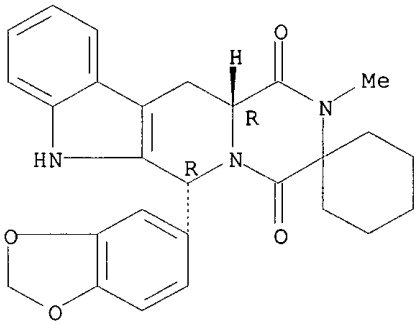
RN 395665-42-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-(hydroxymethyl)-, (3R,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



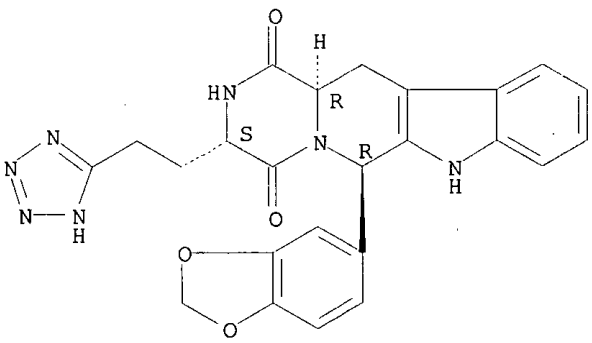
RN 395665-43-7 CAPLUS
CN Spiro[cyclohexane-1,3'(4'H)-pyrazino[1',2':1,6]pyrido[3,4-b]indole]-1',4'(2'H)-dione, 6'-(1,3-benzodioxol-5-yl)-6',7',12',12'a-tetrahydro-2'-methyl-, (6'R,12'aR)- (9CI) (CA INDEX NAME)

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)

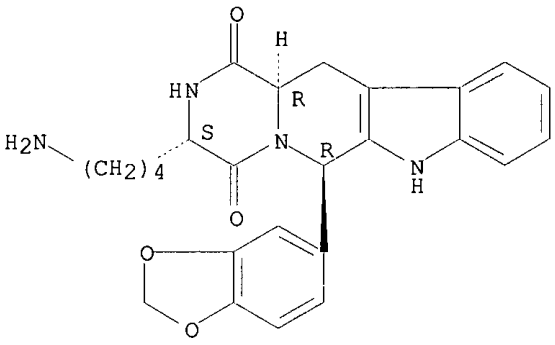
Absolute stereochemistry.



RN 395665-49-3 CAPLUS

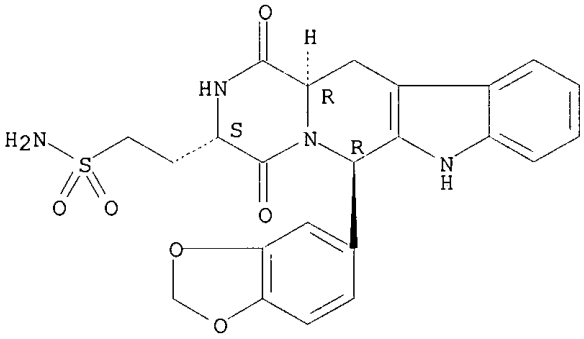
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 3-(4-aminobutyl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



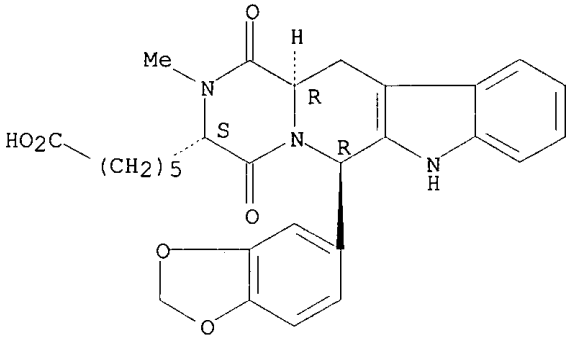
RN 395665-51-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-ethanesulfonamide, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



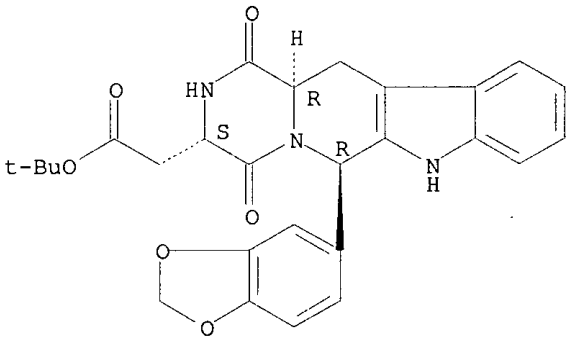
RN 395665-53-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-hexanoic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-2-methyl-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



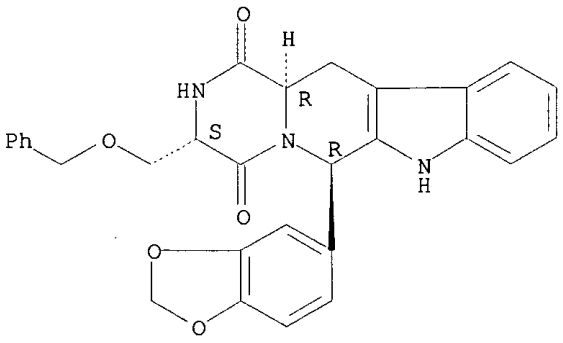
RN 395665-55-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 1,1-dimethylethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

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)

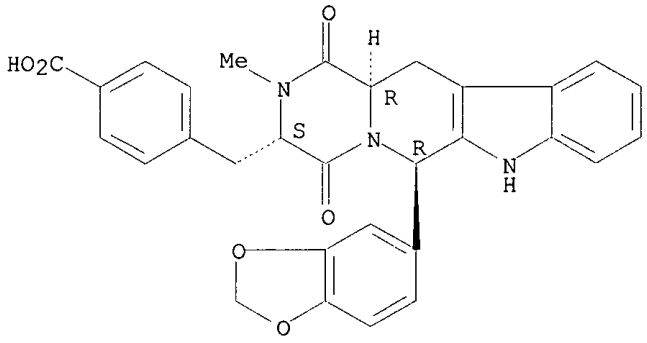
Absolute stereochemistry.



RN 395665-59-5 CAPLUS

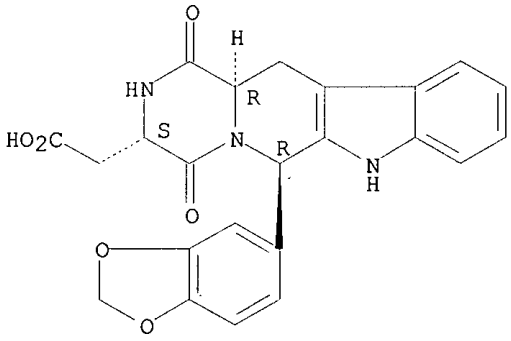
CN Benzoic acid, 4-[[(3S,6R,12aR)-6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-2-methyl-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-3-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



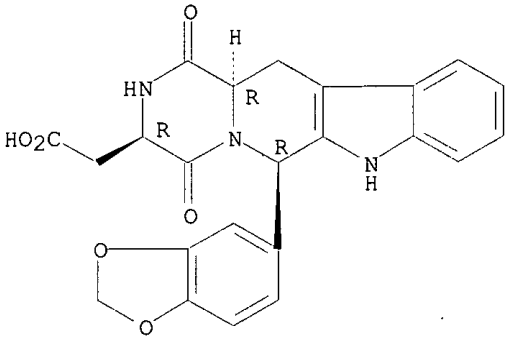
RN 395665-61-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



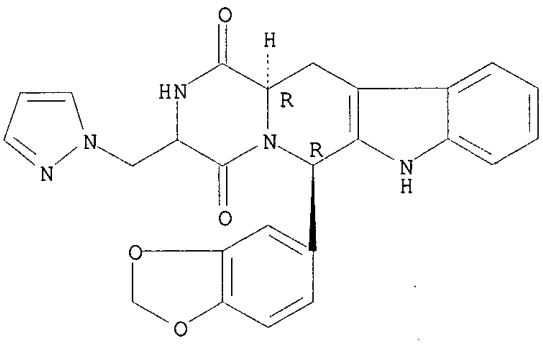
RN 395665-63-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3R,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



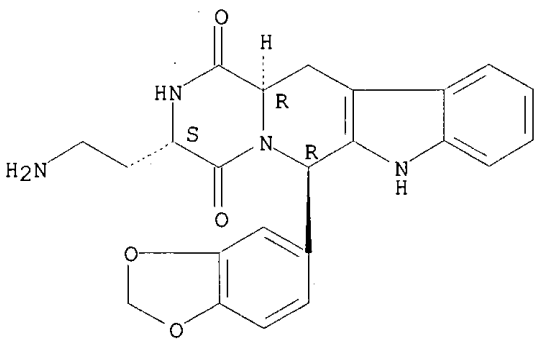
RN 395665-65-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-(1H-pyrazol-1-ylmethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

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)

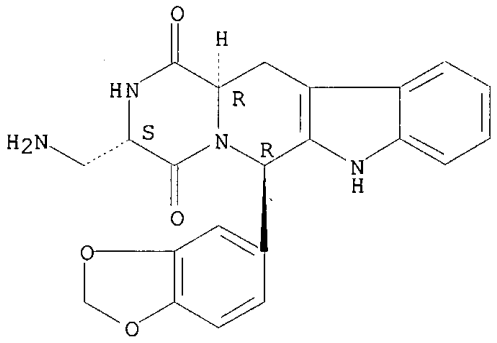
Absolute stereochemistry.



RN 395665-69-7 CAPLUS

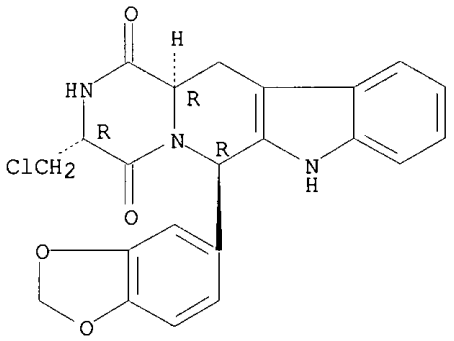
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 3-(aminomethyl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



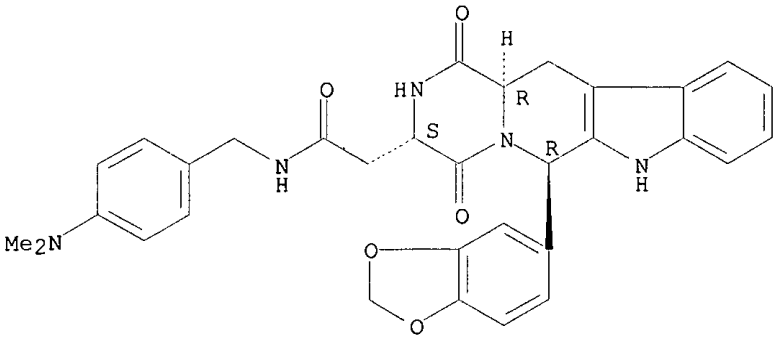
RN 395665-70-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-3-(chloromethyl)-2,3,6,7,12,12a-hexahydro-, (3R,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



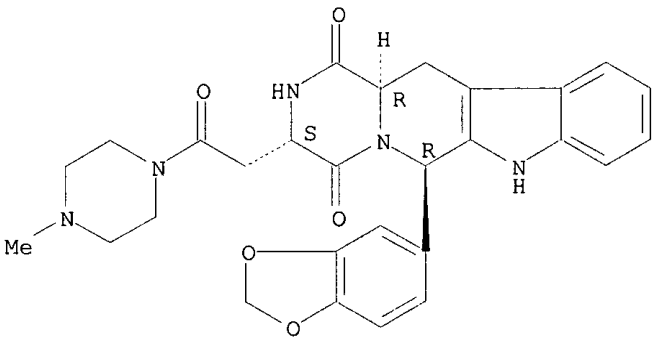
RN 395665-71-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetamide, 6-(1,3-benzodioxol-5-yl)-N-[[4-(dimethylamino)phenyl]methyl]-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



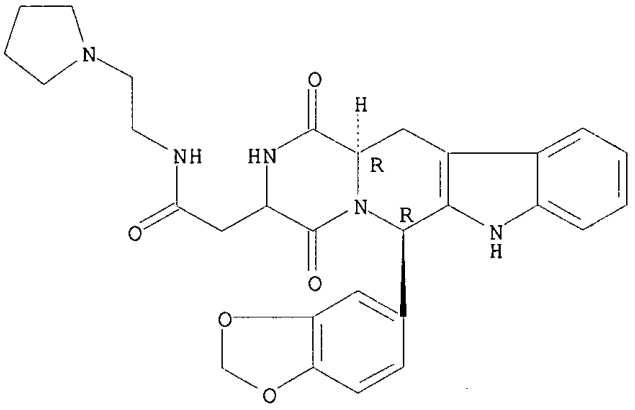
RN 395665-72-2 CAPLUS
CN Piperazine, 1-[[(3S,6R,12aR)-6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-3-yl]acetyl]-4-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



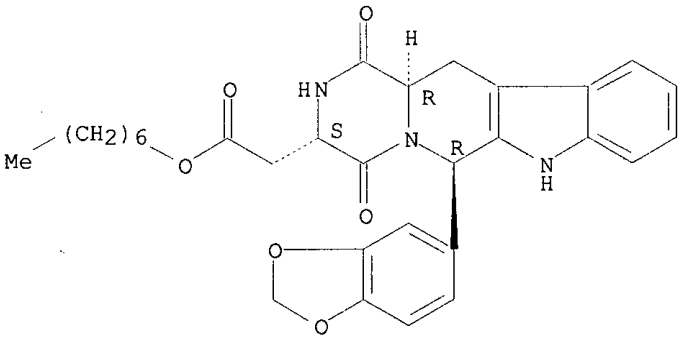
RN 395665-73-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetamide, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-N-[2-(1-pyrrolidinyl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



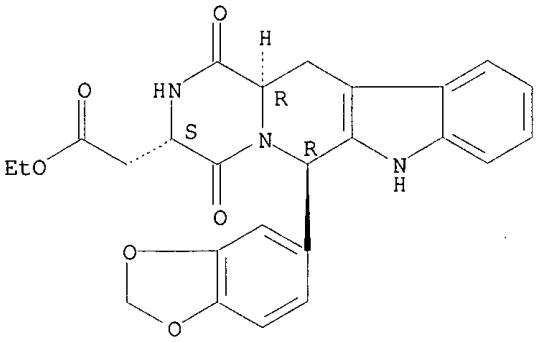
RN 395665-75-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, heptyl ester, (3S,6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



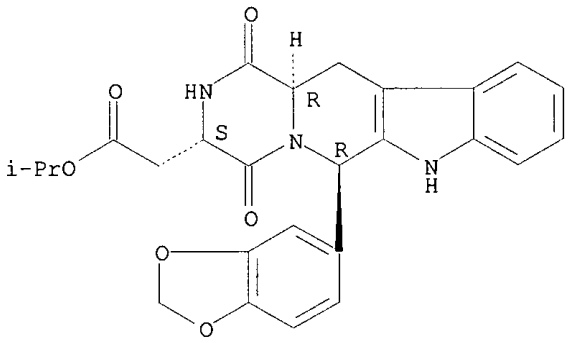
RN 395665-76-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, ethyl ester, (3S,6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



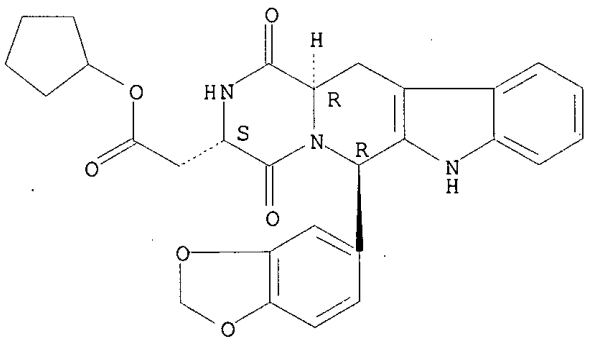
RN 395665-77-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 1-methylethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

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)

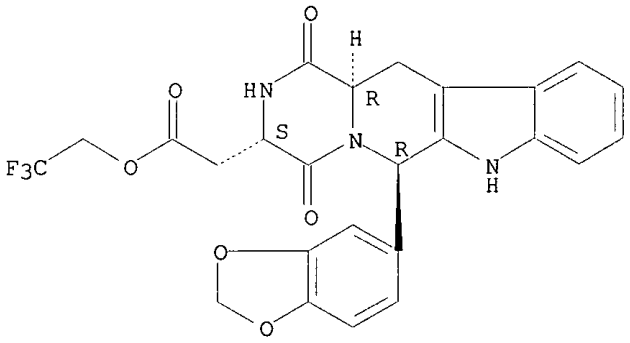
Absolute stereochemistry.



RN 395665-79-9 CAPLUS

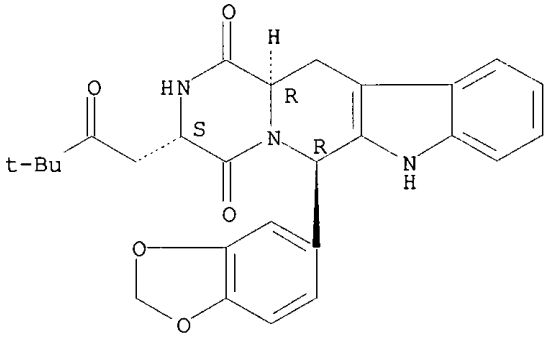
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, 2,2,2-trifluoroethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



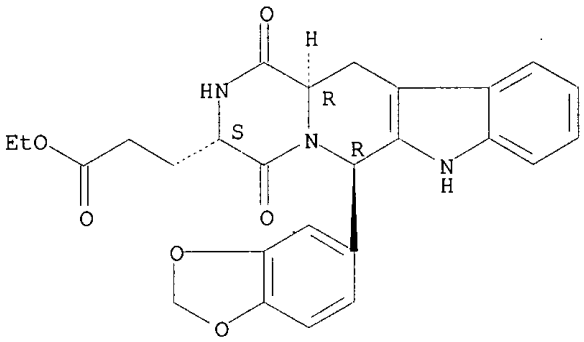
RN 395665-80-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-3-(3,3-dimethyl-2-oxobutyl)-2,3,6,7,12,12a-hexahydro-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



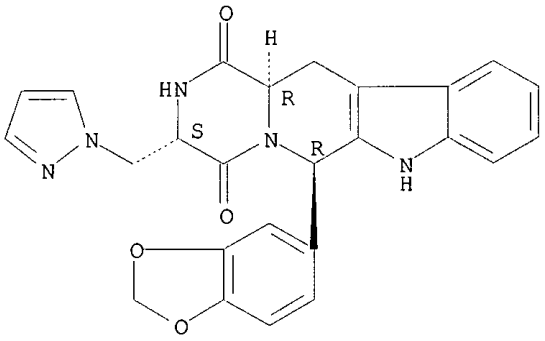
RN 395665-81-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-propanoic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-, ethyl ester, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



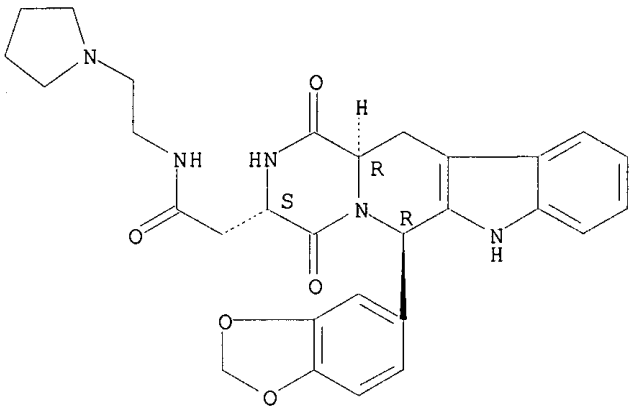
RN 395665-91-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-(1H-pyrazol-1-ylmethyl)-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



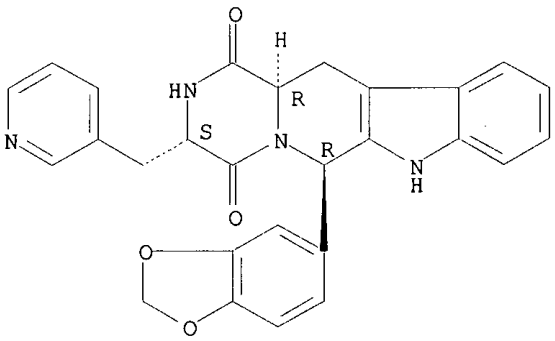
RN 395665-95-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-3-acetamide, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-1,4-dioxo-N-[2-(1-pyrrolidinyl)ethyl]-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



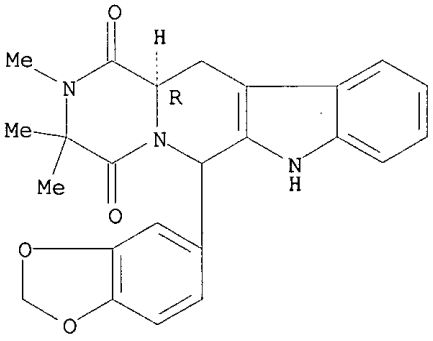
RN 395665-96-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-(3-pyridinylmethyl)-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

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

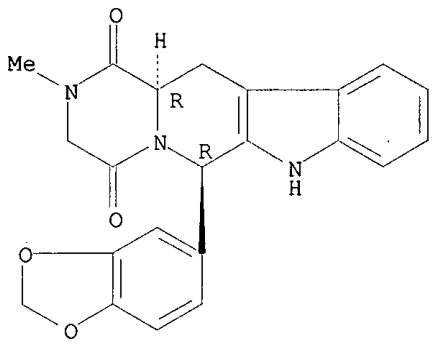
OTHER SOURCE(S): MARPAT 136:96099

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)

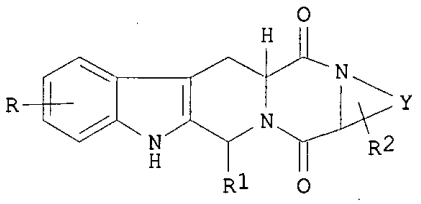
Absolute stereochemistry. Rotation (+).



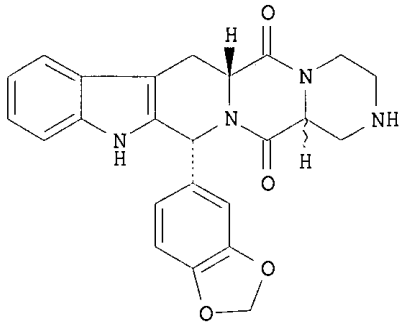
L12 ANSWER 9 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:10477 CAPLUS
DOCUMENT NUMBER: 136:85829
TITLE: preparation of ring fused pyrazinopyridoindole derivatives as cyclic GMP-specific phosphodiesterase inhibitors
INVENTOR(S): Orme, Mark W.; Sawyer, Jason Scott
PATENT ASSIGNEE(S): Lilly Icos 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



I



II

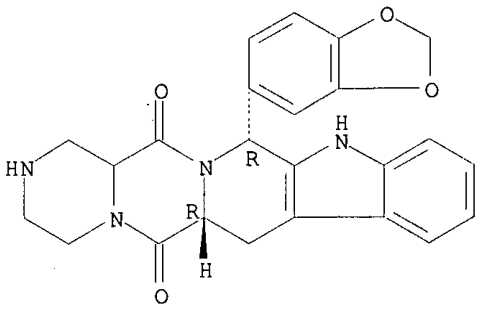
AB The title compds. I (R = halo, C1-6-alkyl; R1 = a nonocyclic arom. ring selected from benzene, thiophene, furan, and pyridine, and an optionally substituted bicyclic ring wherein the fused ring is a 5- or 6-membered ring and optionally with one or two heteroatoms selected from O, S, and N; Y = a 3-, 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

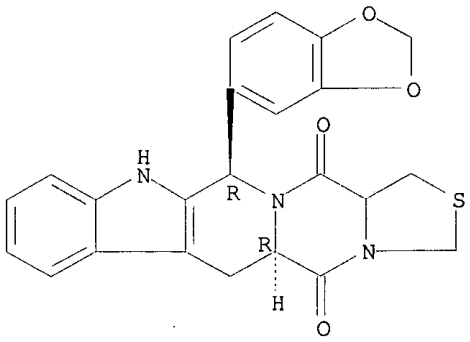
CN 6H-Pyrazino[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-6,15(2H)-dione, 13-(1,3-benzodioxol-5-yl)-1,3,4,6a,7,12,13,15a-octahydro-, (6aR,13R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



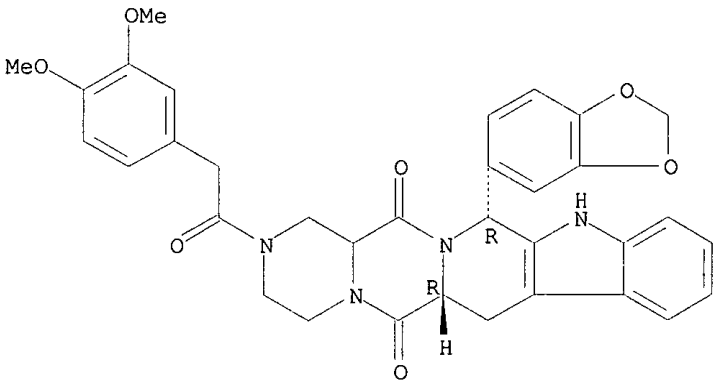
RN 385765-03-7 CAPLUS
CN 3H,5H,14H-Thiazolo[3'',4'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,5a,6,11,12,14a-hexahydro-, (5aR,12R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



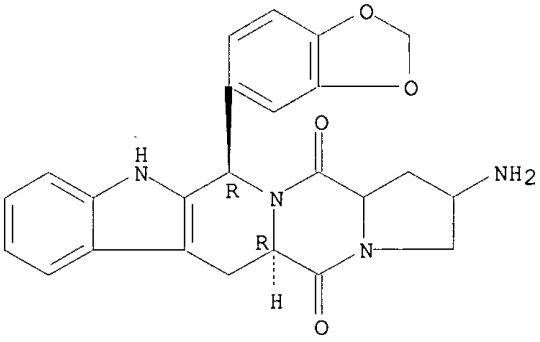
IT **385765-04-8P 385765-05-9P 385765-06-0P**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of ring fused pyrazinopyridoindole derivs. as cyclic GMP-specific phosphodiesterase 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.



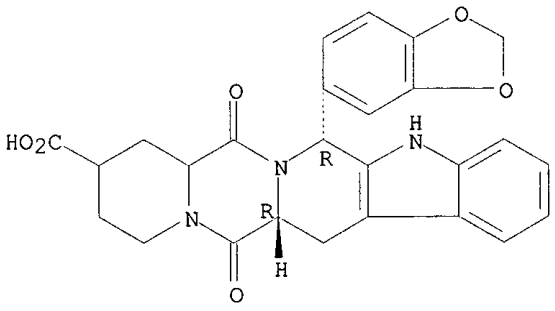
RN 385765-05-9 CAPLUS
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 2-amino-12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R)- (9CI) (CA INDEX NAME)

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 *

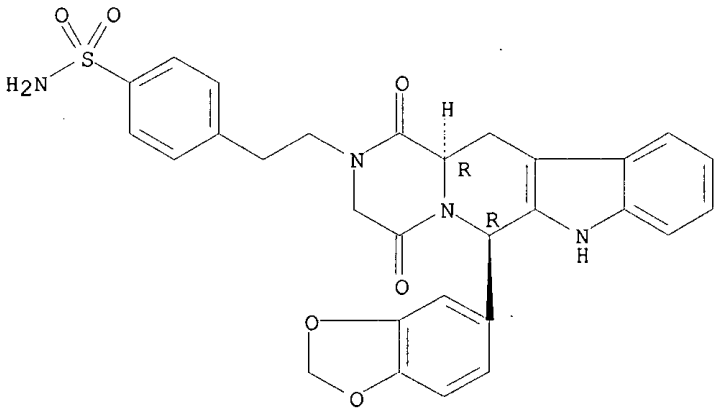
AB The pyrazinopyridoindolediones I (R = halo, C1-6-alkyl; R1 = aryl, heteroaryl, amino, R4O, R4CO, R4SO, R4SO2, C1-4-alkylene-CO2R4, C1-4-alkylenehetreroaryl, sulfamoyl, cyano, NO2, CO-C1-4-alkyleneheteroaryl, C1-4-alkylene-OR4, etc.; R2 = monocyclic arom. ring consisting of benzene, thiophene, furan, 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)

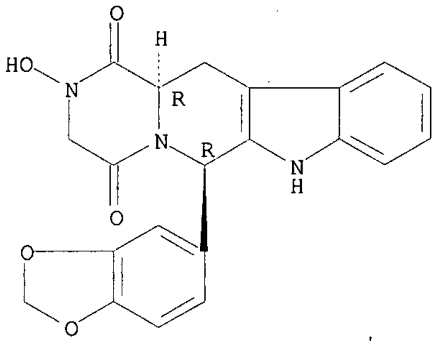
RN 385769-78-8 CAPLUS
CN Benzenesulfonamide, 4-[2-[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



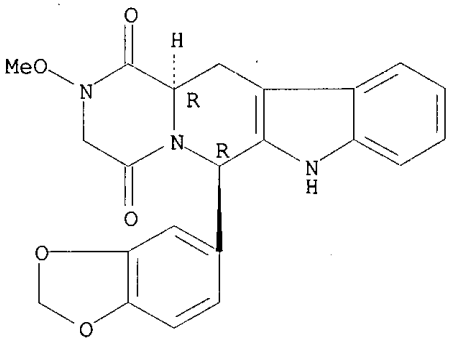
RN 385769-80-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-hydroxy-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



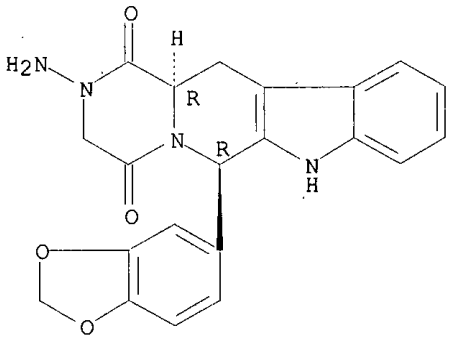
RN 385769-82-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methoxy-, (6R,12aR)- (9CI) (CA INDEX NAME)

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)

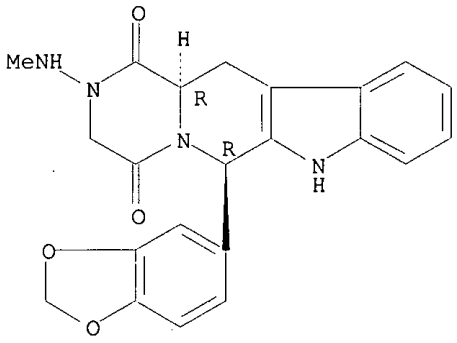
Absolute stereochemistry.



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)-

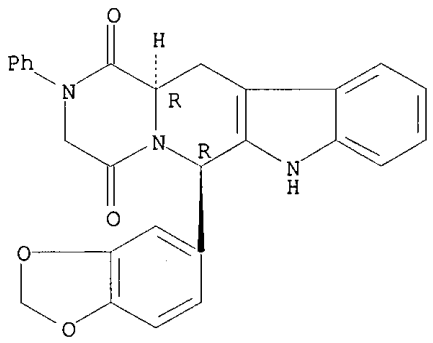
2,3,6,7,12,12a-hexahydro-2-(methylamino)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



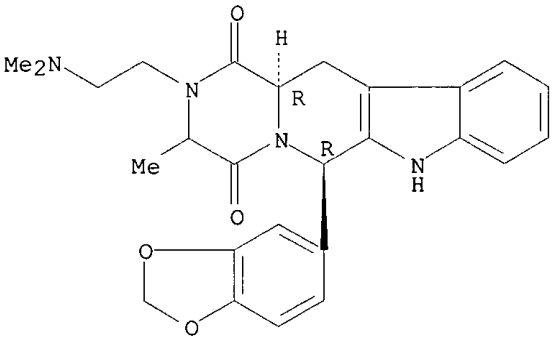
RN 385769-88-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-phenyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



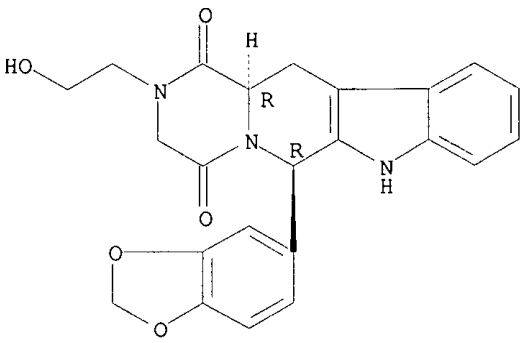
RN 385769-90-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-(dimethylamino)ethyl]-2,3,6,7,12,12a-hexahydro-3-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



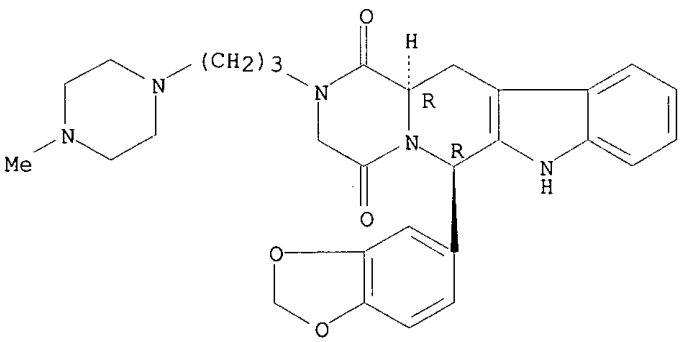
RN 385769-94-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-hydroxyethyl)-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

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)

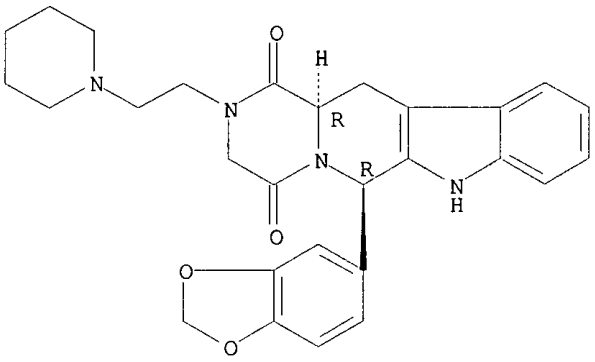
Absolute stereochemistry.



RN 385770-00-3 CAPLUS

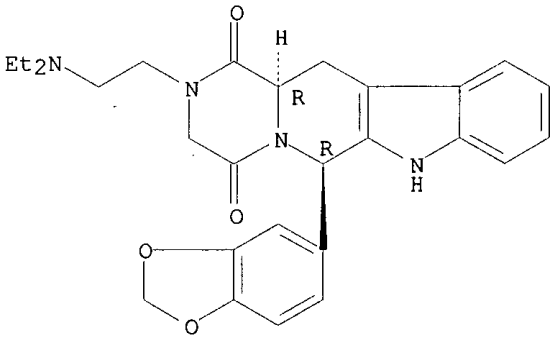
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(1-piperidinyl)ethyl]-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



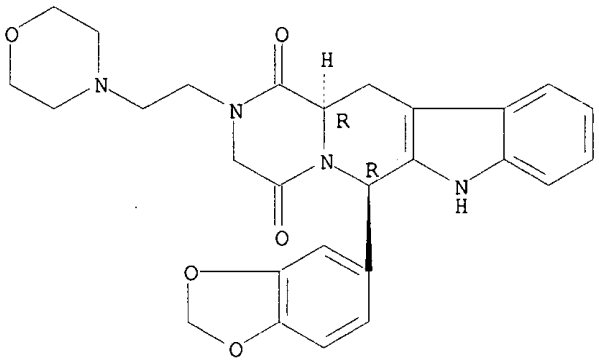
RN 385770-01-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-(diethylamino)ethyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



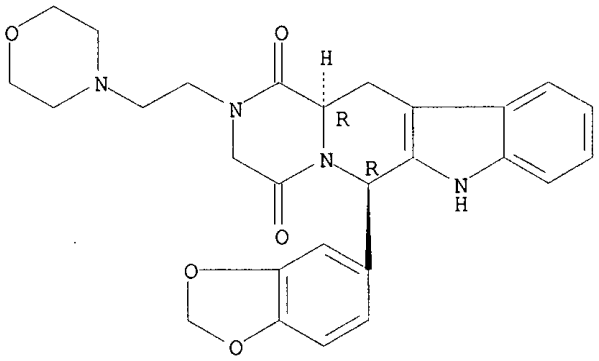
RN 385770-03-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(4-morpholinyl)ethyl]-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



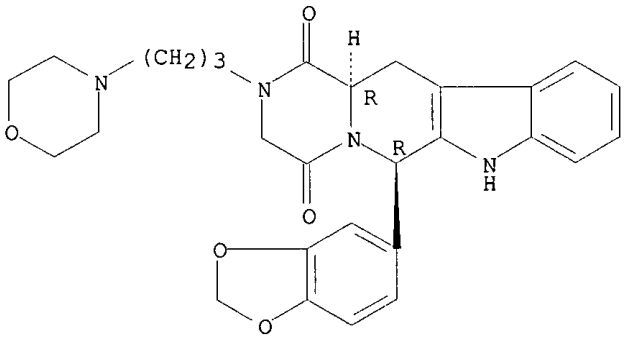
RN 385770-04-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(4-morpholinyl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



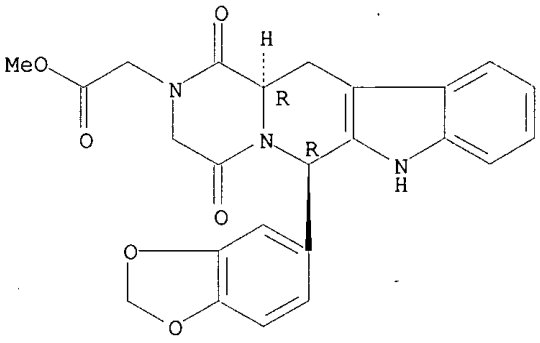
RN 385770-06-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[3-(4-morpholinyl)propyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



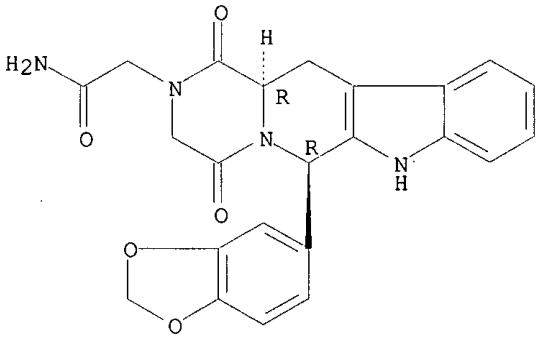
RN 385770-07-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, methyl ester, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



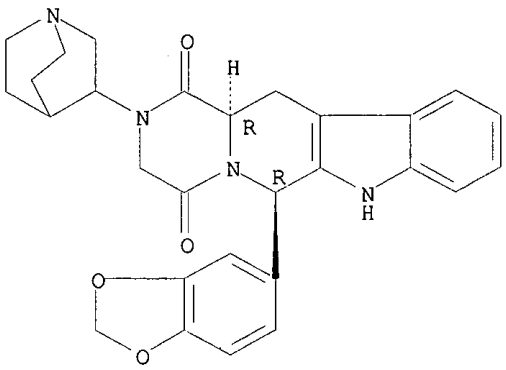
RN 385770-09-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



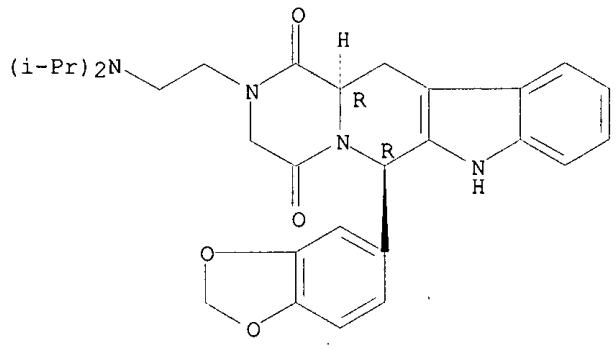
RN 385770-11-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-(1-azabicyclo[2.2.2]oct-3-yl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



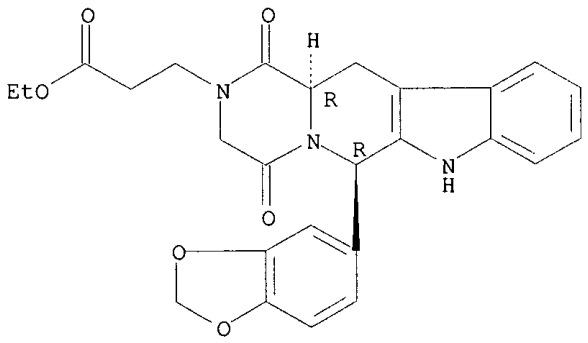
RN 385770-13-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-[bis(1-methylethyl)amino]ethyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



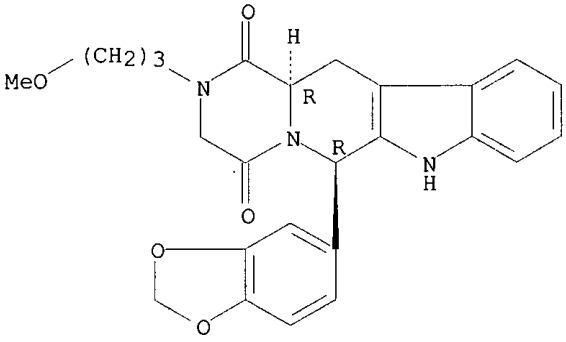
RN 385770-15-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-propanoic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, ethyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



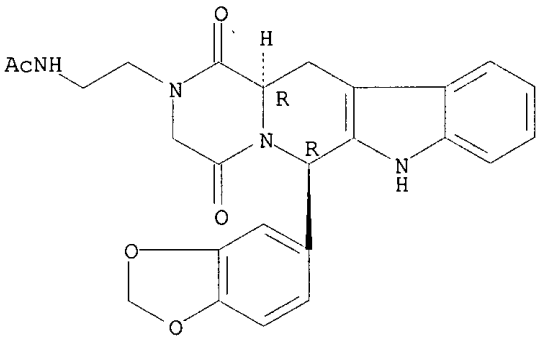
RN 385770-18-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(3-methoxypropyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



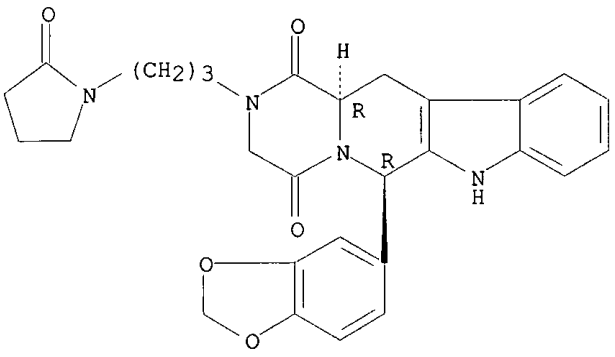
RN 385770-20-7 CAPLUS
CN Acetamide, N-[2-[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



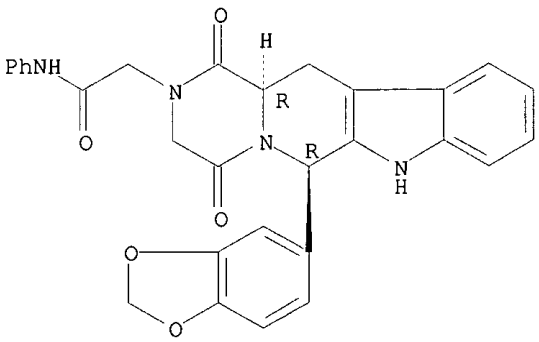
RN 385770-22-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[3-(2-oxo-1-pyrrolidinyl)propyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



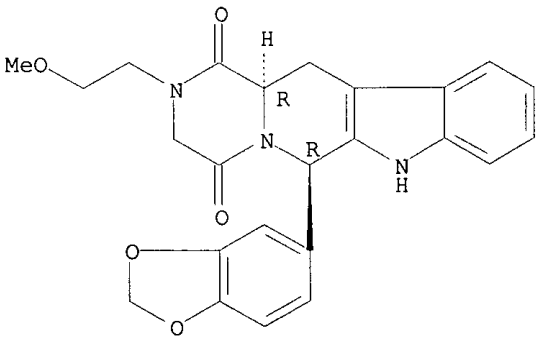
RN 385770-24-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-N-phenyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



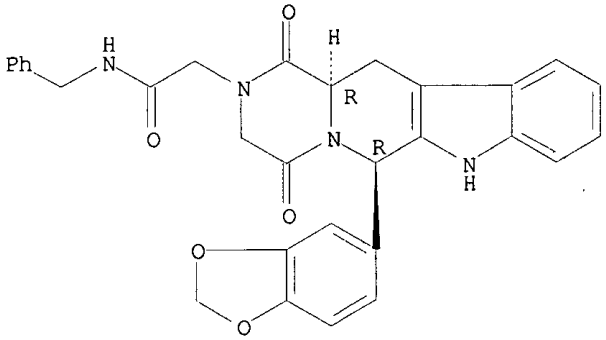
RN 385770-26-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-methoxyethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



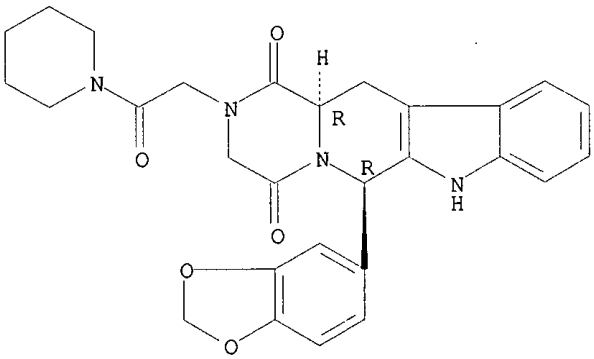
RN 385770-28-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-N-(phenylmethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



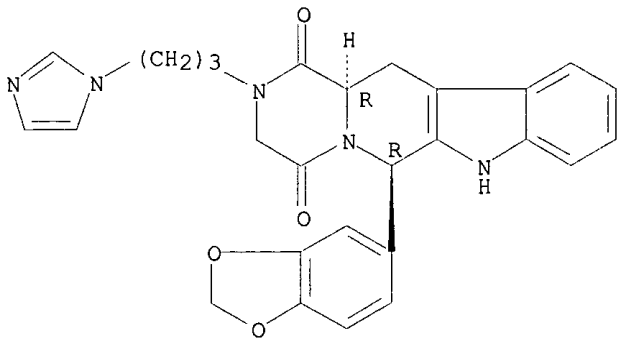
RN 385770-29-6 CAPLUS
CN Piperidine, 1-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



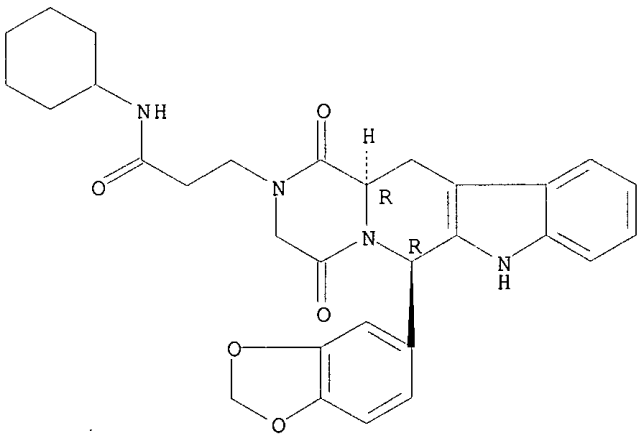
RN 385770-30-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[3-(1H-imidazol-1-yl)propyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



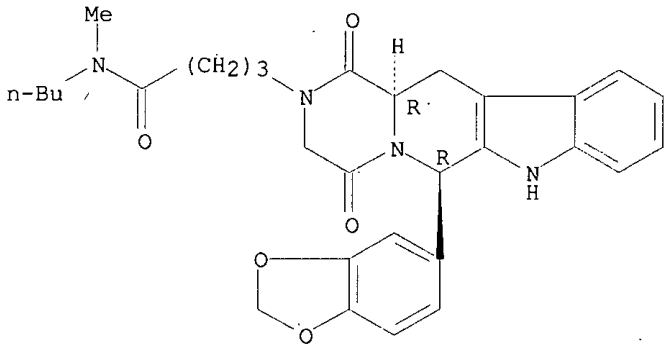
RN 385770-31-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-propanamide, 6-(1,3-benzodioxol-5-yl)-N-cyclohexyl-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



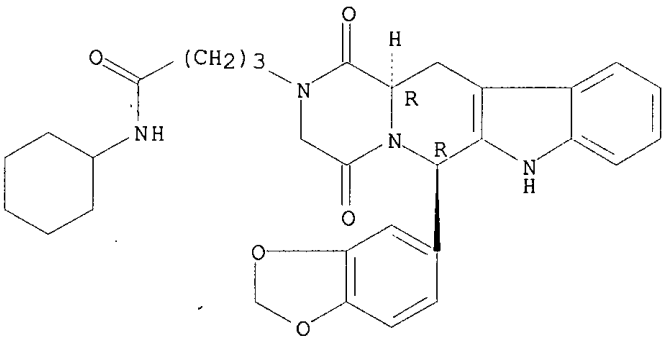
RN 385770-32-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-butanamide, 6-(1,3-benzodioxol-5-yl)-N-butyl-3,4,6,7,12,12a-hexahydro-N-methyl-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



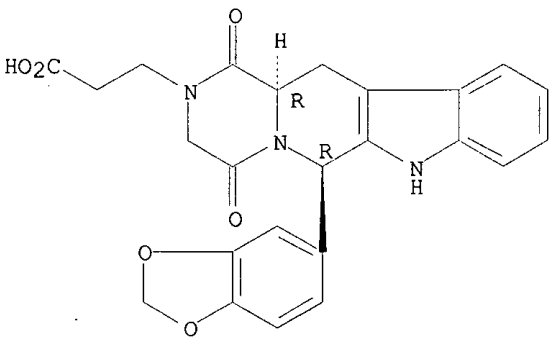
RN 385770-34-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-butanamide, 6-(1,3-benzodioxol-5-yl)-N-cyclohexyl-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



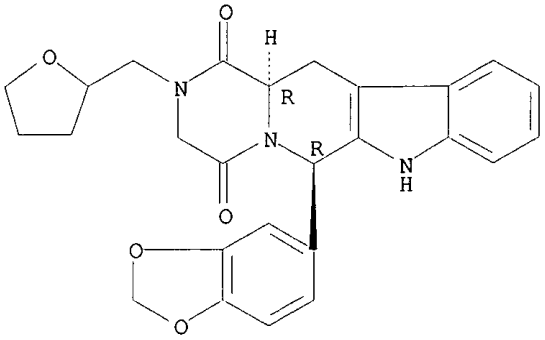
RN 385770-36-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-propanoic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



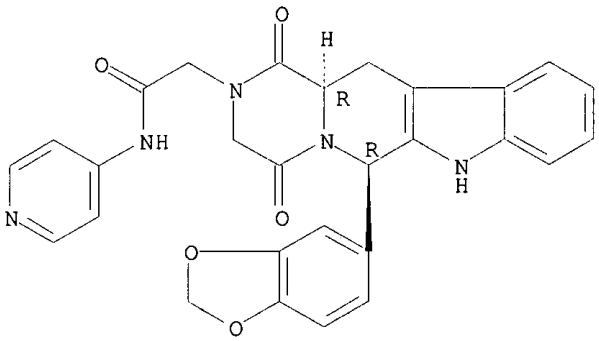
RN 385770-38-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[(tetrahydro-2-furanyl)methyl]-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



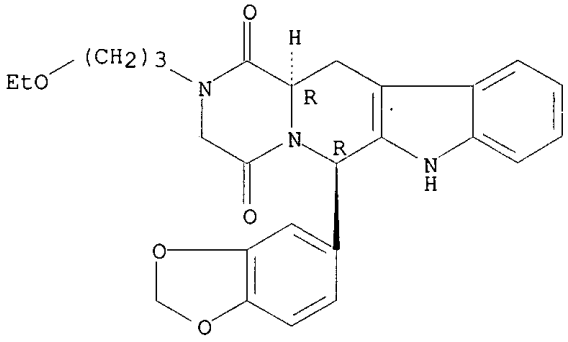
RN 385770-40-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-N-4-pyridinyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



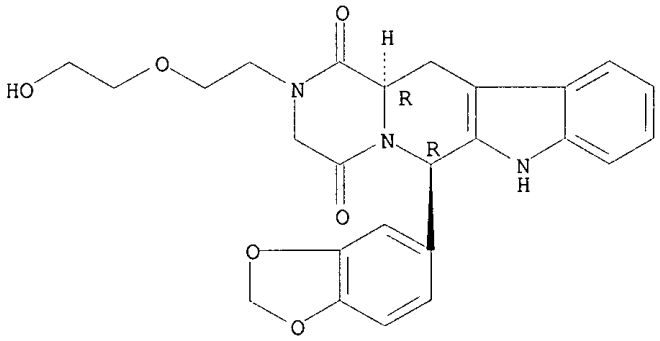
RN 385770-41-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(3-ethoxypropyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



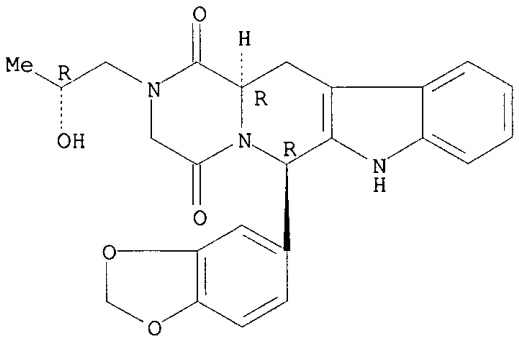
RN 385770-43-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(2-hydroxyethoxy)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

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)

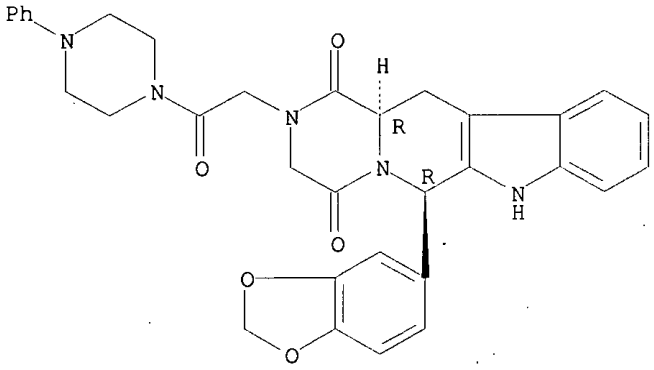
Absolute stereochemistry.



RN 385770-46-7 CAPLUS

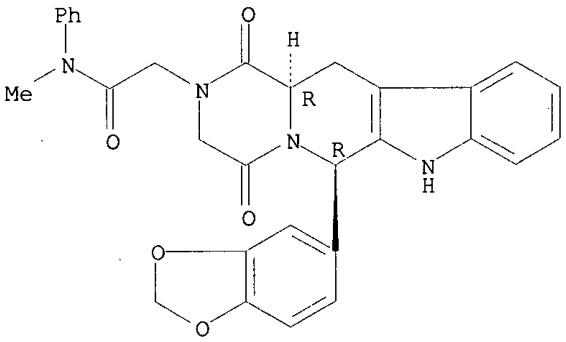
CN Piperazine, 1-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]acetyl]-4-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



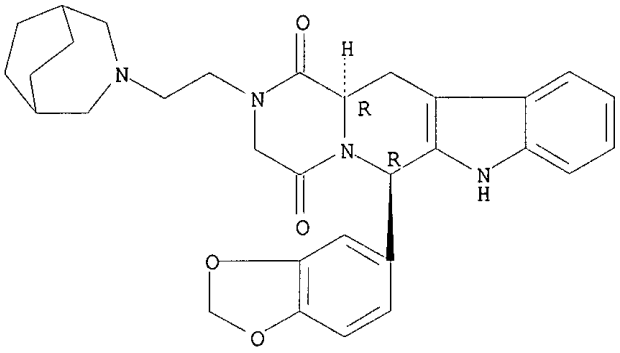
RN 385770-48-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-N-methyl-1,4-dioxo-N-phenyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



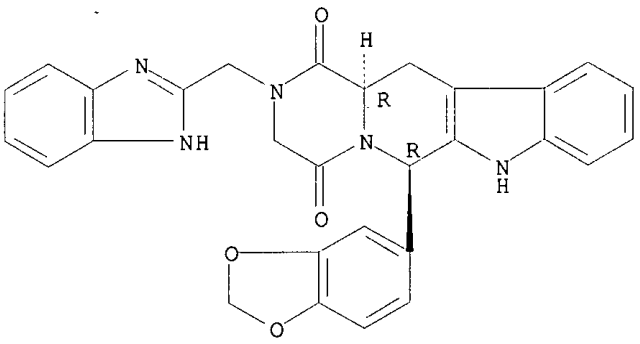
RN 385770-49-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-[2-(3-azabicyclo[3.2.2]non-3-yl)ethyl]-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



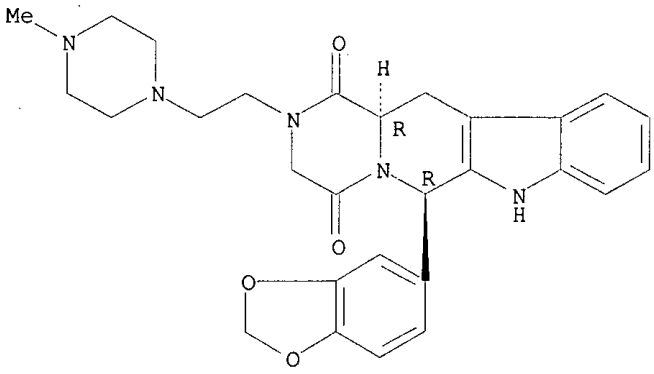
RN 385770-50-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-(1H-benzimidazol-2-ylmethyl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



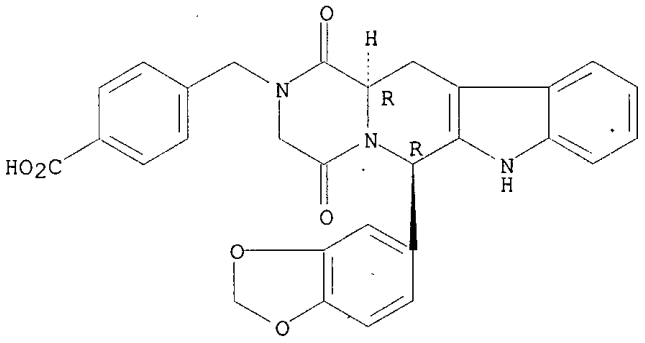
RN 385770-52-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(4-methyl-1-piperazinyl)ethyl]-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



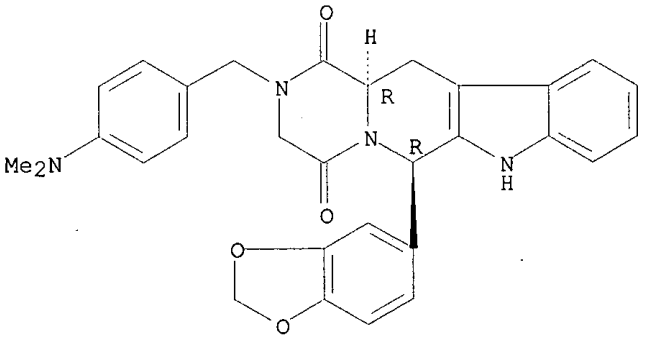
RN 385770-54-7 CAPLUS
CN Benzoic acid, 4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



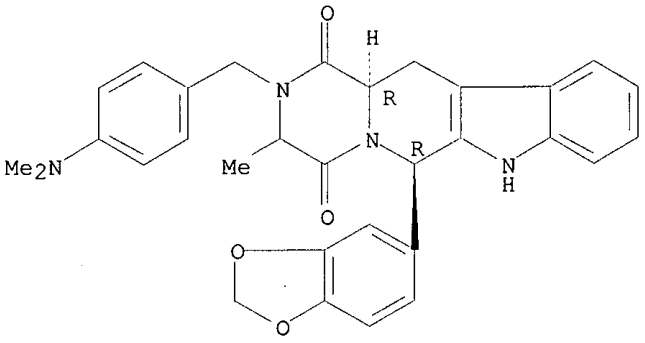
RN 385770-56-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[[4-(dimethylamino)phenyl]methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



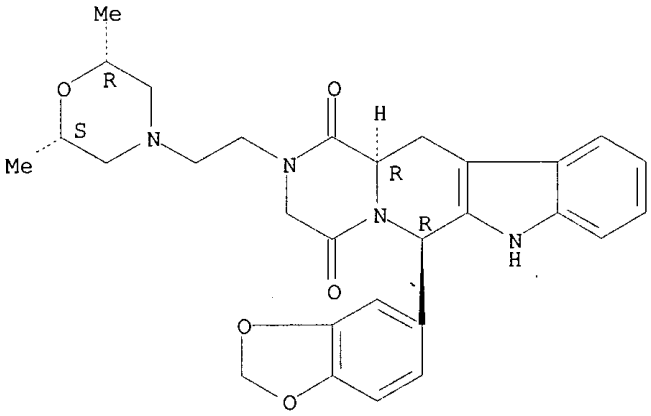
RN 385770-57-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[[4-(dimethylamino)phenyl]methyl]-2,3,6,7,12,12a-hexahydro-3-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



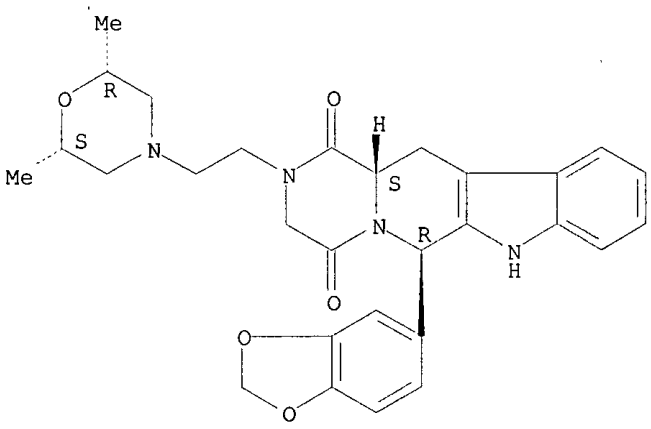
RN 385770-58-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-[(2R,6S)-2,6-dimethyl-4-morpholinyl]ethyl]-2,3,6,7,12,12a-hexahydro-, (6S,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



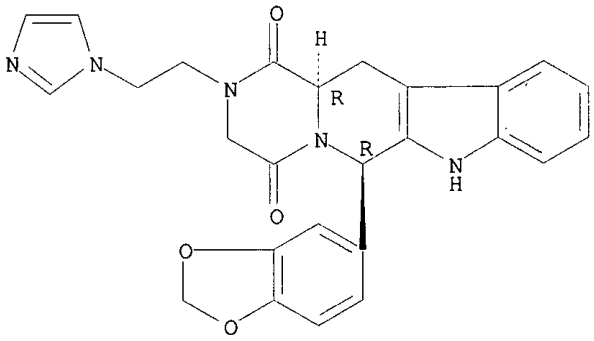
RN 385770-60-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-[(2R,6S)-2,6-dimethyl-4-morpholinyl]ethyl]-2,3,6,7,12,12a-hexahydro-, (6S,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



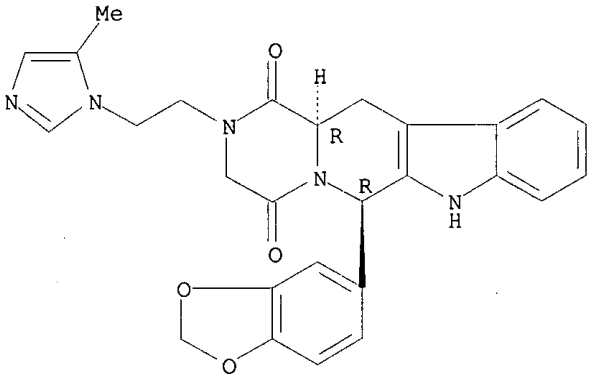
RN 385770-62-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(1H-imidazol-1-yl)ethyl]-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



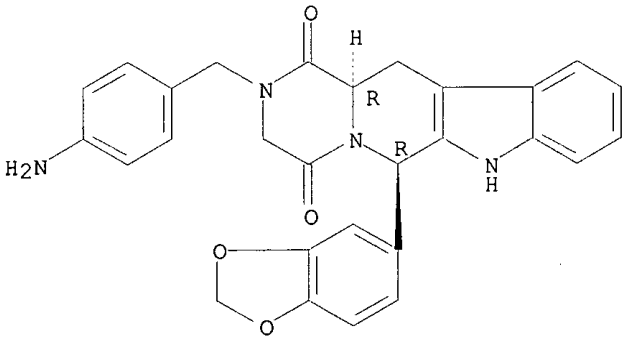
RN 385770-64-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(5-methyl-1H-imidazol-1-yl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



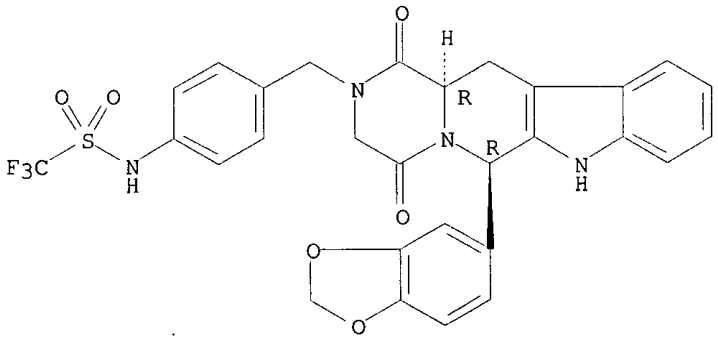
RN 385770-66-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-[(4-aminophenyl)methyl]-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



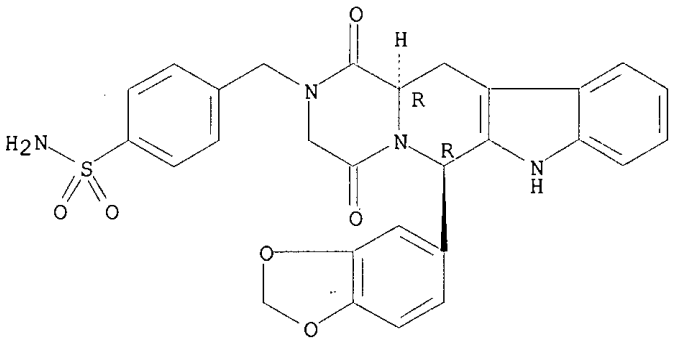
RN 385770-68-3 CAPLUS
CN Methanesulfonamide, N-[4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]phenyl]-1,1,1-trifluoro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



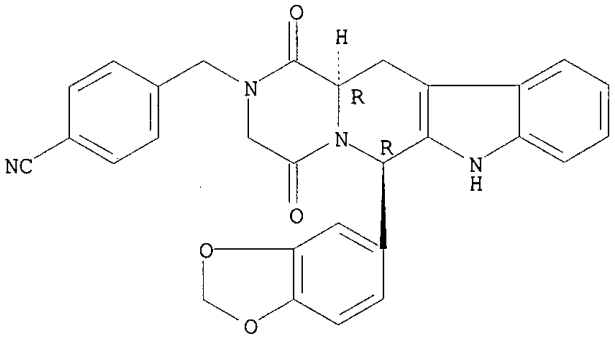
RN 385770-70-7 CAPLUS
CN Benzenesulfonamide, 4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



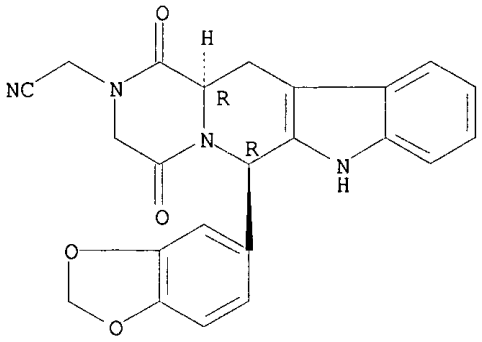
RN 385770-72-9 CAPLUS
CN Benzonitrile, 4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



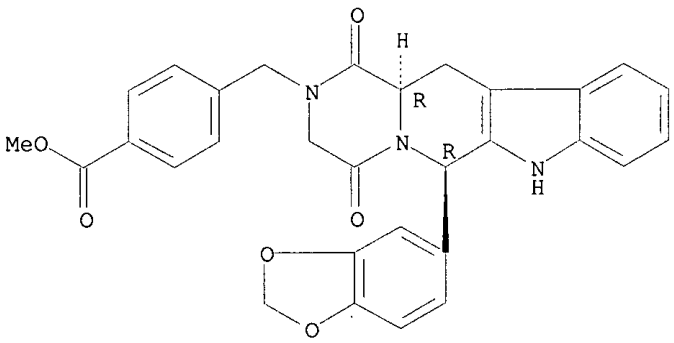
RN 385770-73-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetonitrile, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



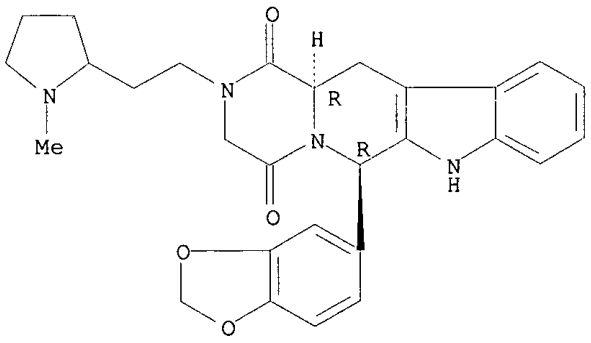
RN 385770-75-2 CAPLUS
CN Benzoic acid, 4-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]-, methyl ester (9CI) (CA INDEX NAME)

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)

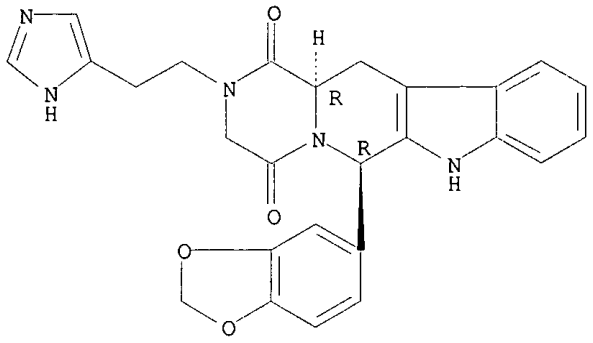
Relative stereochemistry.



RN 385770-77-4 CAPLUS

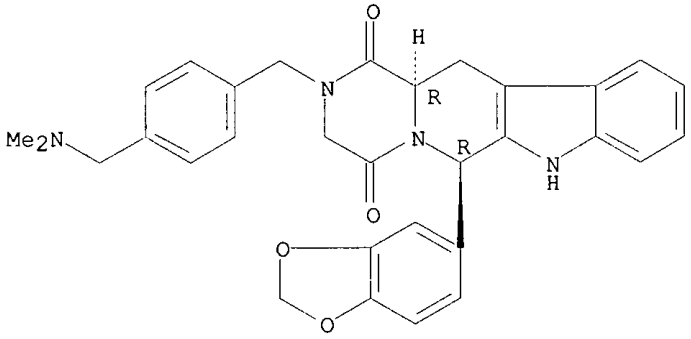
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(1H-imidazol-4-yl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



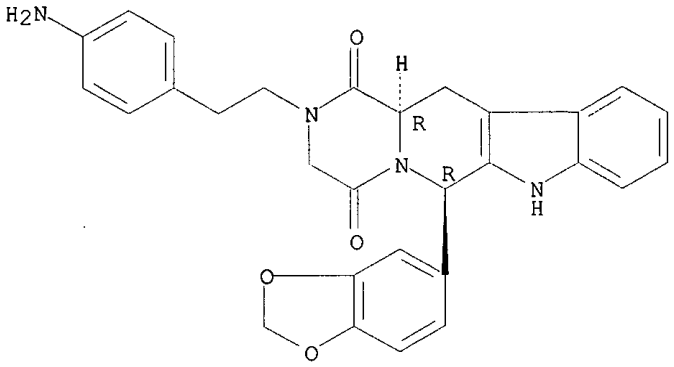
RN 385770-78-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[[4-[(dimethylamino)methyl]phenyl]methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



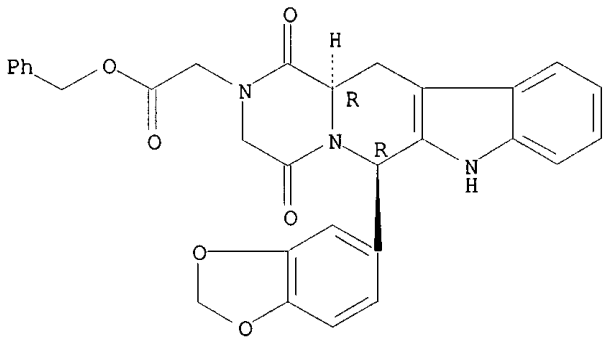
RN 385770-79-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 2-[2-(4-aminophenyl)ethyl]-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



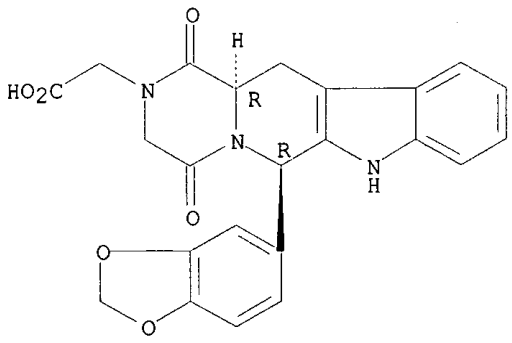
RN 385770-80-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, phenylmethyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



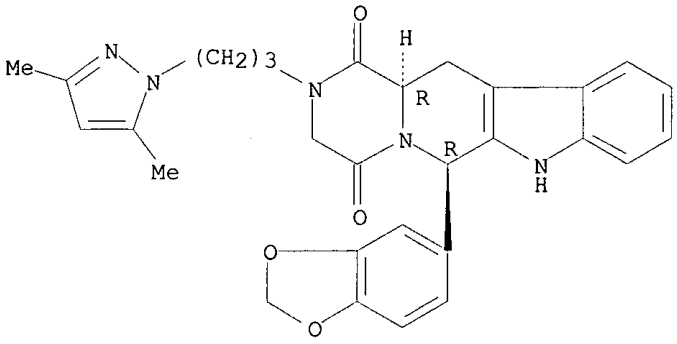
RN 385770-82-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



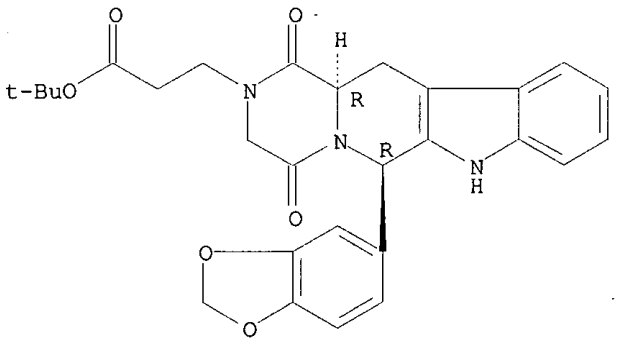
RN 385770-83-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[3-(3,5-dimethyl-1H-pyrazol-1-yl)propyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



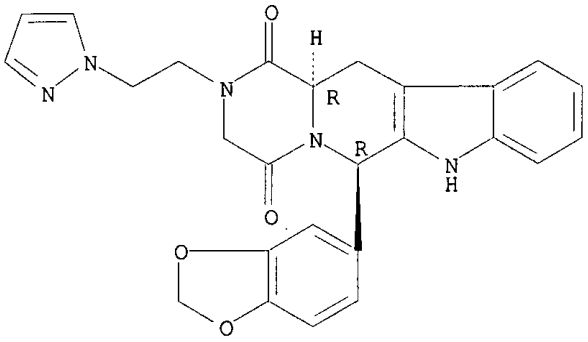
RN 385770-85-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-propanoic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, 1,1-dimethylethyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



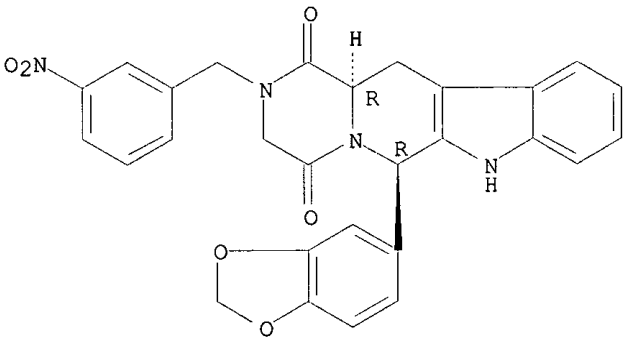
RN 385770-89-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(1H-pyrazol-1-yl)ethyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



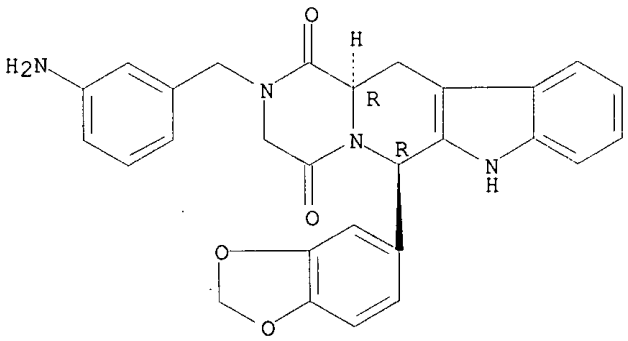
RN 385770-91-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[(3-nitrophenyl)methyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

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)

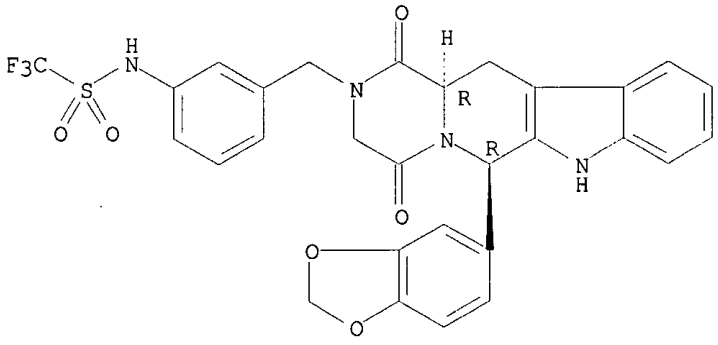
Absolute stereochemistry.



RN 385770-93-4 CAPLUS

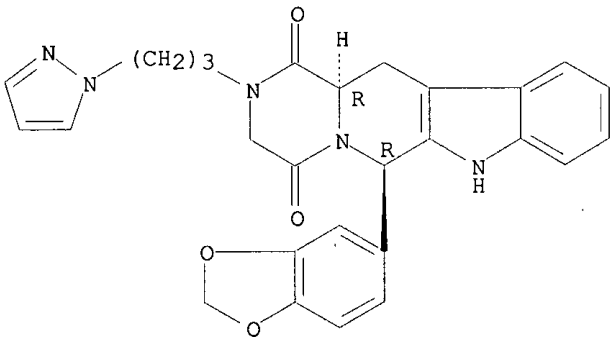
CN Methanesulfonamide, N-[3-[[(6R,12aR)-6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxopyrazino[1',2':1,6]pyrido[3,4-b]indol-2(1H)-yl]methyl]phenyl]-1,1,1-trifluoro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



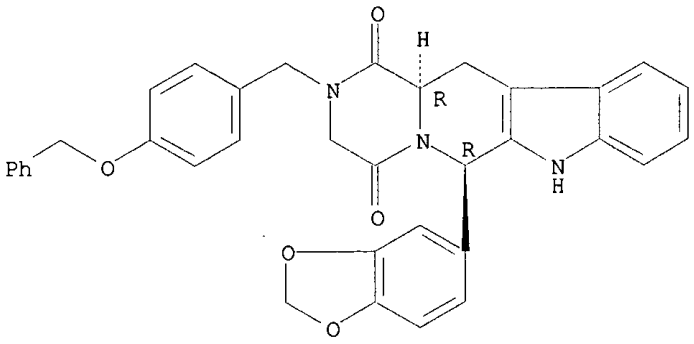
RN 385770-95-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[3-(1H-pyrazol-1-yl)propyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



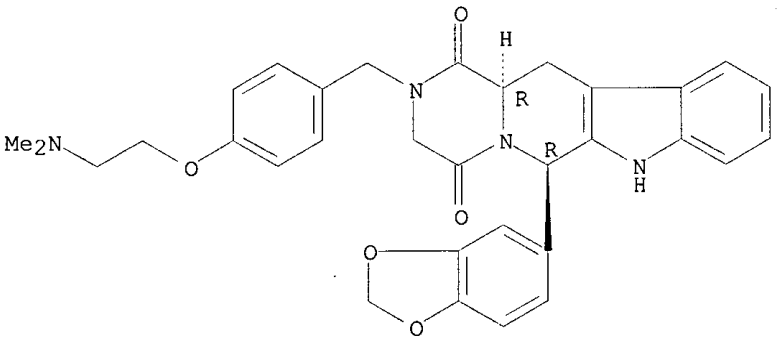
RN 385770-96-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[[4-(phenylmethoxy)phenyl]methyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



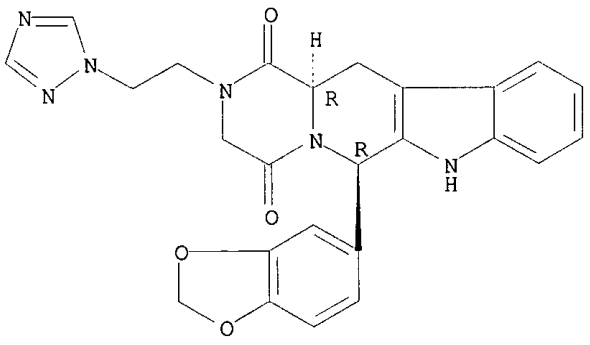
RN 385770-98-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

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)

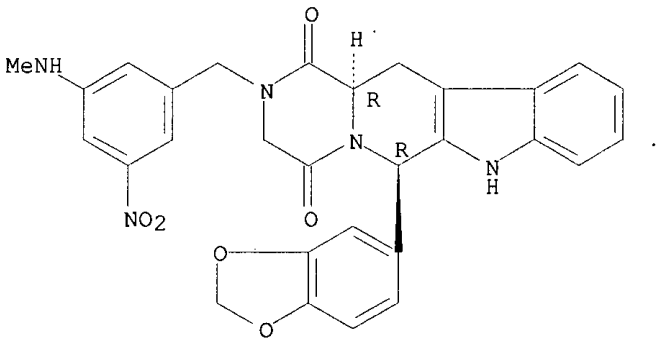
Absolute stereochemistry.



RN 385771-02-8 CAPLUS

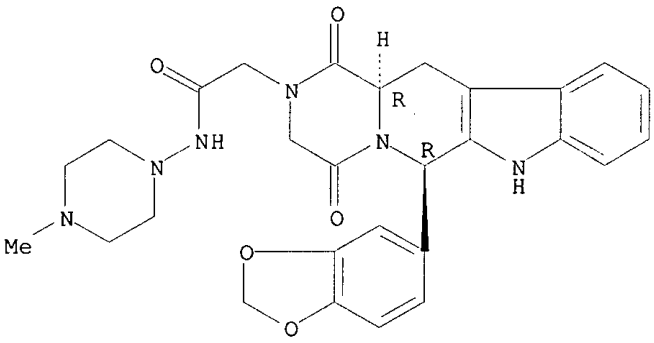
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[[3-(methylamino)-5-nitrophenyl]methyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



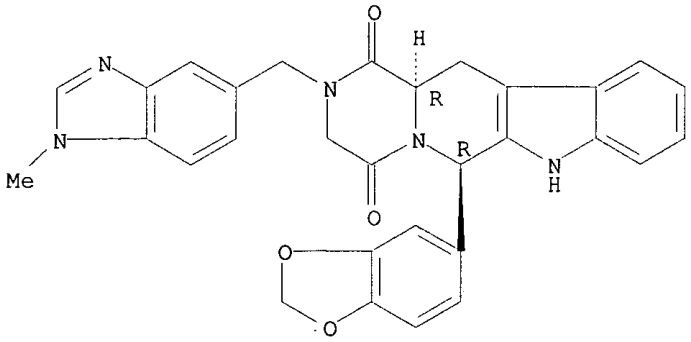
RN 385771-03-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetamide, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-N-(4-methyl-1-piperazinyl)-1,4-dioxo-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



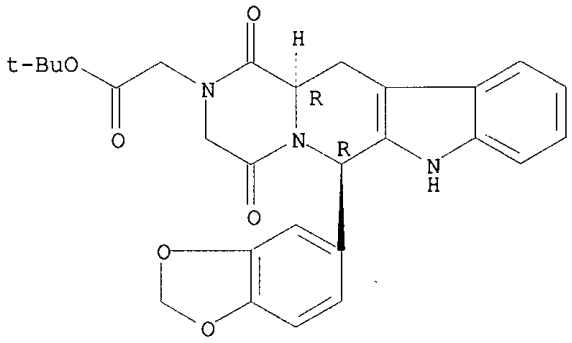
RN 385771-05-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[(1-methyl-1H-benzimidazol-5-yl)methyl]-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



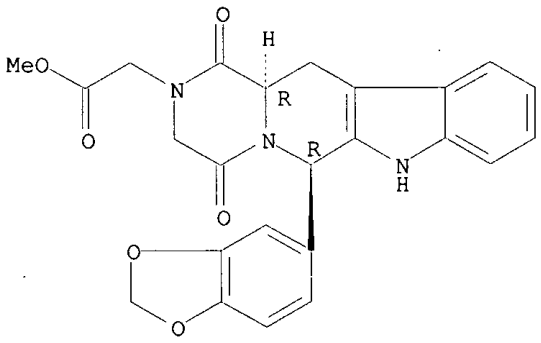
RN 385771-06-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-2(1H)-acetic acid, 6-(1,3-benzodioxol-5-yl)-3,4,6,7,12,12a-hexahydro-1,4-dioxo-, 1,1-dimethylethyl ester, (6R,12aR)- (9CI) (CA INDEX NAME)

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)

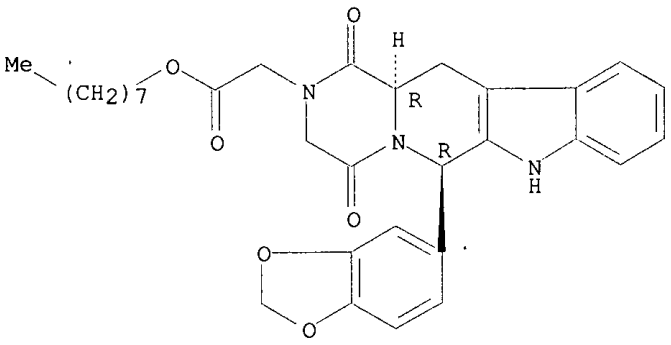
Absolute stereochemistry.



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

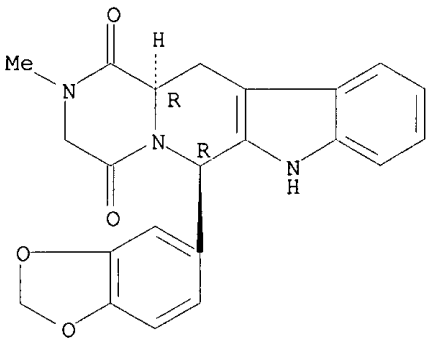
PRIORITY APPLN. INFO.: US 1999-132036P P 19990430
US 2000-558911 A2 20000426
WO 2000-US11129 W 20000426

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**

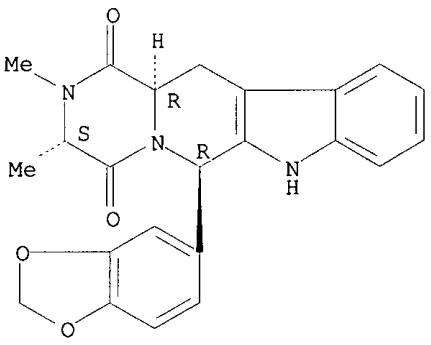
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase 5 inhibitor for daily treatment for erectile dysfunction)
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (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

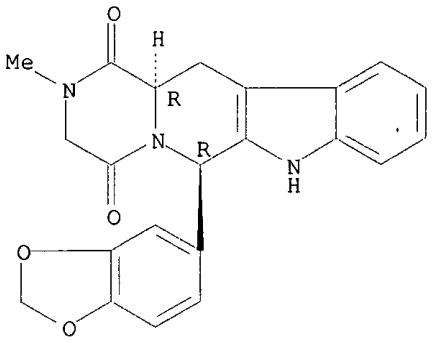
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

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 (+).



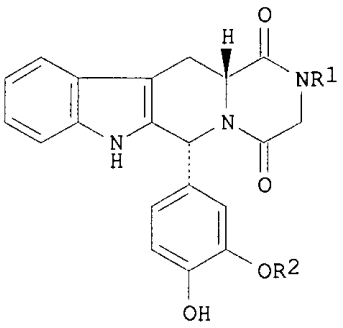
REFERENCE COUNT: 86 THERE ARE 86 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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

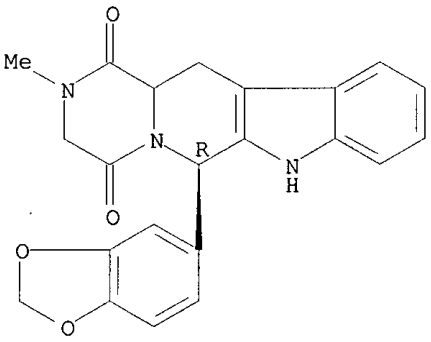
AB The title compds. I [R1 = C1-6 alkyl; R2 = H, Me] were prepd. and use of the compds. as PDE5 inhibitors was described.. E.g., (6R,12aR)-6-(3,4-dihydroxyphenyl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione was prepd. I may be used for male erectile dysfunction or 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

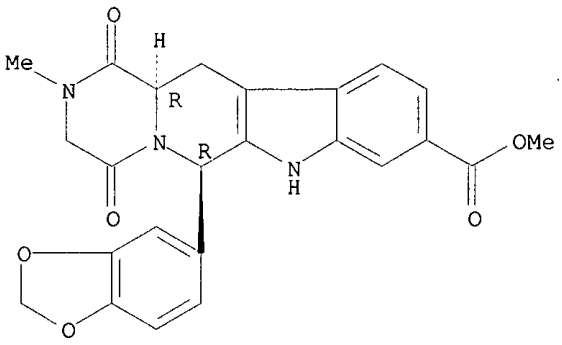
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

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)

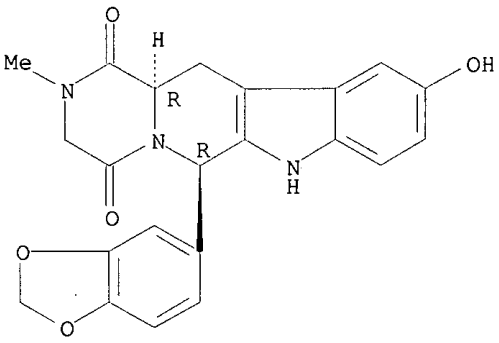
Relative stereochemistry.



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)

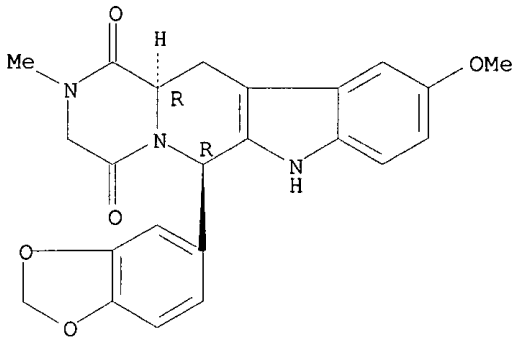
RN 379234-74-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-10-hydroxy-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



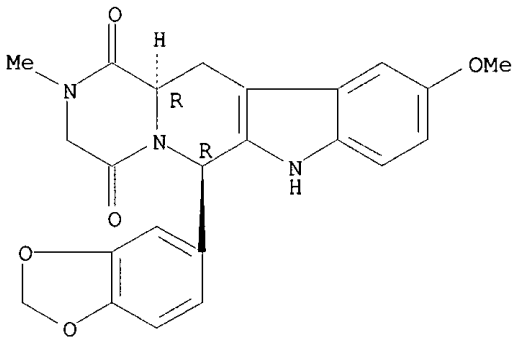
RN 379234-78-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-10-methoxy-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



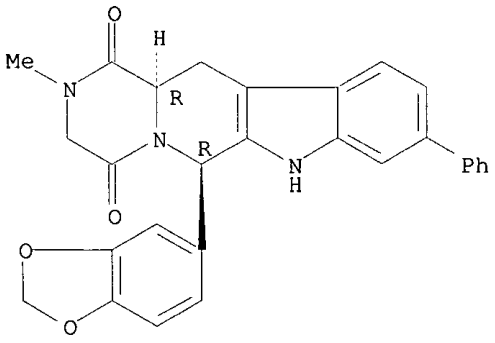
RN 379234-82-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-10-methoxy-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

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)

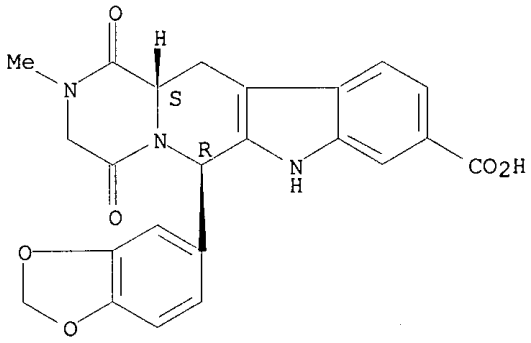
Relative stereochemistry.



RN 379234-98-7 CAPLUS

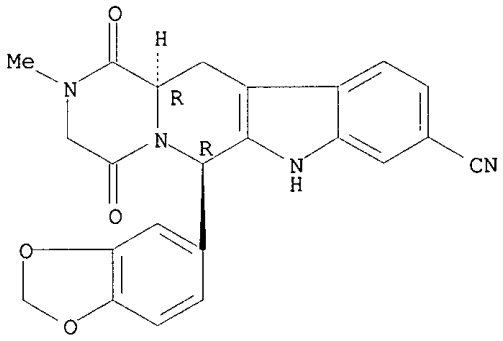
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-9-carboxylic acid, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-2-methyl-1,4-dioxo-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



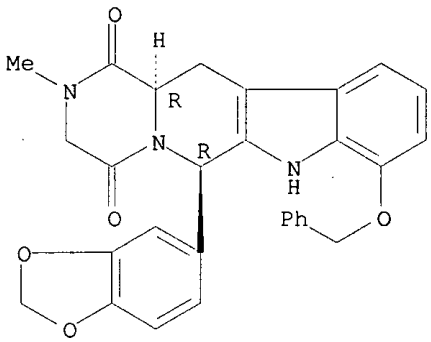
RN 379235-06-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-9-carbonitrile, 6-(1,3-benzodioxol-5-yl)-1,2,3,4,6,7,12,12a-octahydro-2-methyl-1,4-dioxo-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



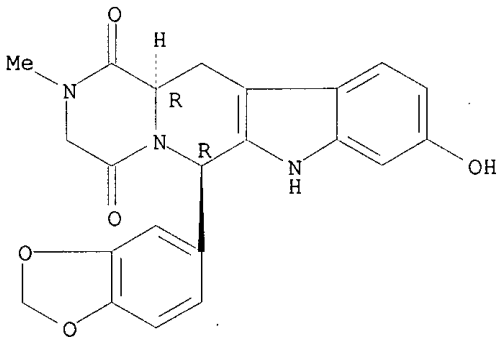
RN 379235-11-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-8-(phenylmethoxy)-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



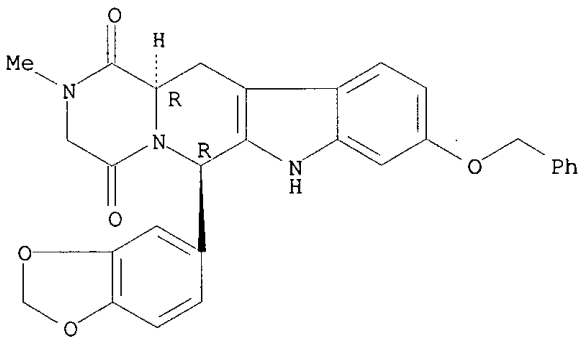
RN 379235-12-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-9-hydroxy-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

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)

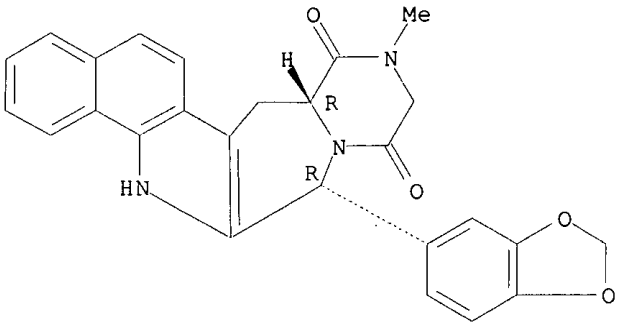
Relative stereochemistry.



RN 379235-14-0 CAPLUS

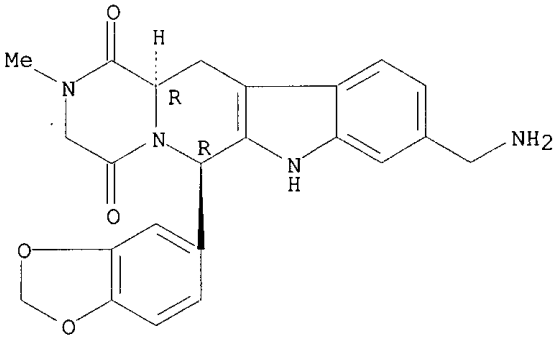
CN Benzo[g]pyrazino[1',2':1,6]pyrido[3,4-b]indole-8,11-dione, 13-(1,3-benzodioxol-5-yl)-7,7a,9,10,13,14-hexahydro-9-methyl-, (7aR,13R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



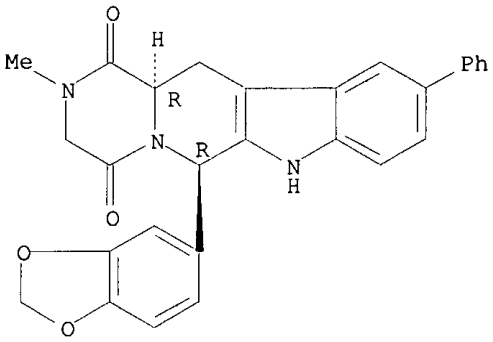
RN 379235-15-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 9-(aminomethyl)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



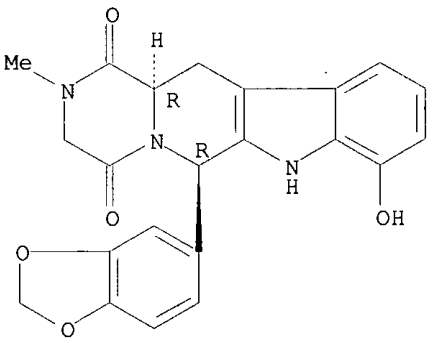
RN 379235-16-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-10-phenyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



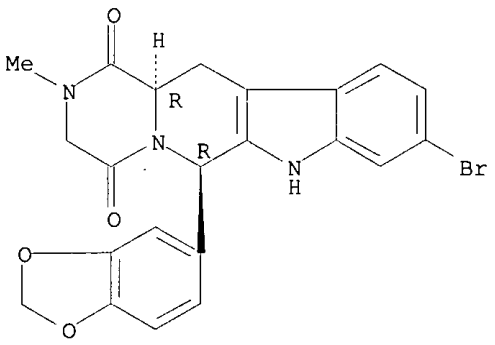
RN 379235-17-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-8-hydroxy-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

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

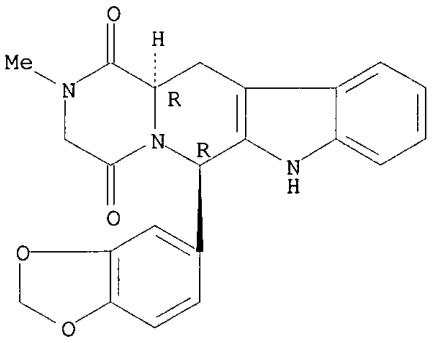
AB The invention relates to phosphodiesterase (PDE) enzyme inhibitors and to their use in pharmaceutical articles of manuf. In particular, the invention relates to potent inhibitors of cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase type 5 (PDE5) that, when incorporated into a pharmaceutical 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)

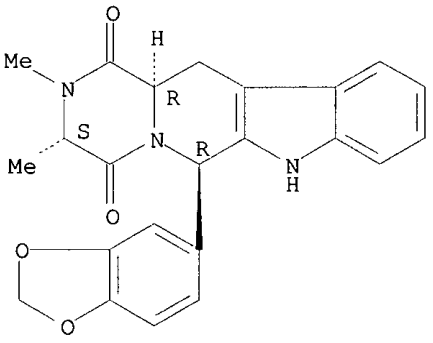
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

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

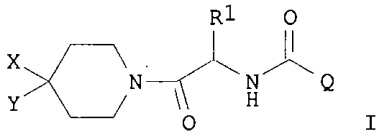
PATENT INFORMATION:

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

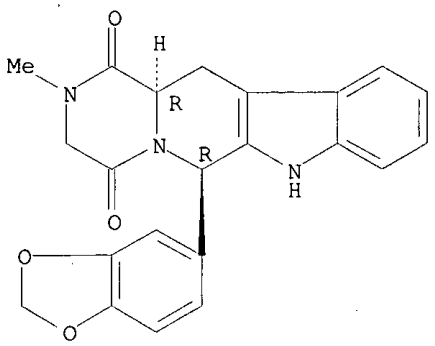
AB Title compds. [I; Q = (substituted) (fused) piperazinyl, morpholinyl, thiomorpholinyl; R1 = H, alkyl, (substituted) cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), etc.; X = (substituted) alkyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), cyano(alkyl), aminosulfonyl(alkyl), 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:

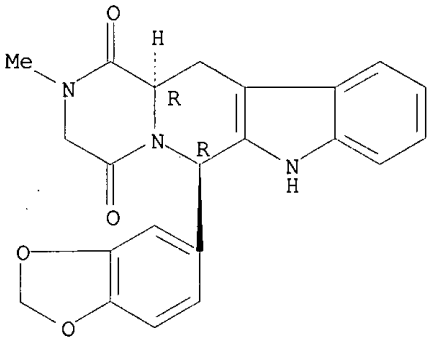
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10004289	A1	20010802	DE 2000-10004289	20000201

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 (+).



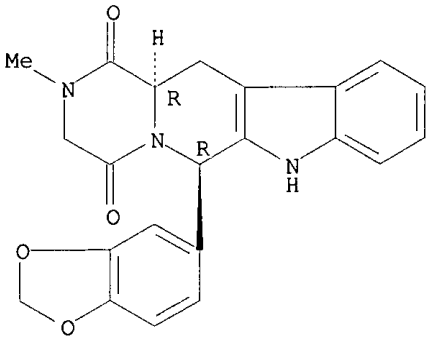
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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

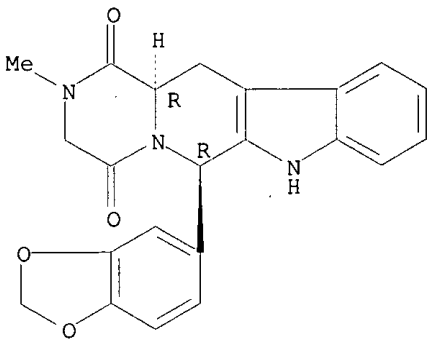
PRIORITY APPLN. INFO.: GB 1999-25970 A 19991102
GB 2000-3235 A 20000211

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 (+).



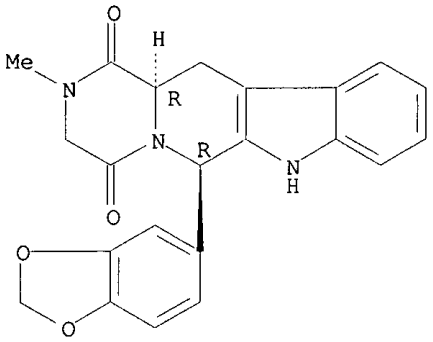
L12 ANSWER 20 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:258390 CAPLUS
DOCUMENT NUMBER: 135:189567
TITLE: IC-351: Treatment of erectile dysfunction treatment of female sexual dysfunction phosphodiesterase 5 inhibitor
AUTHOR(S): Sorbera, L. A.; Martin, L.; Leeson, P. A.; Castaner, J.
CORPORATE 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

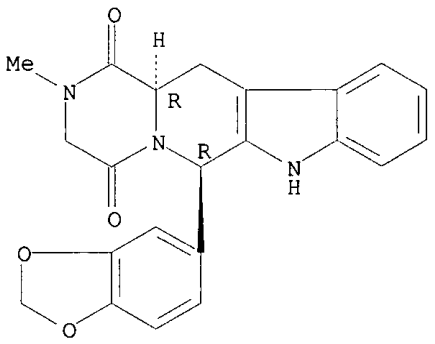
bioavailability of the drug was demonstrated in humans.

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:

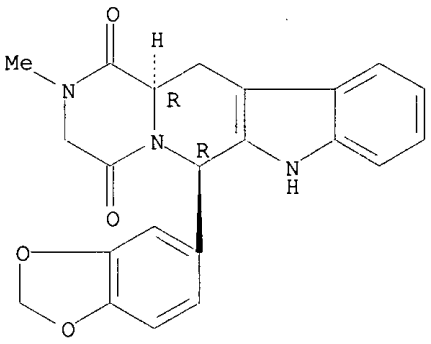
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008687	A1	20010208	WO 2000-US11136	20000426
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, 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

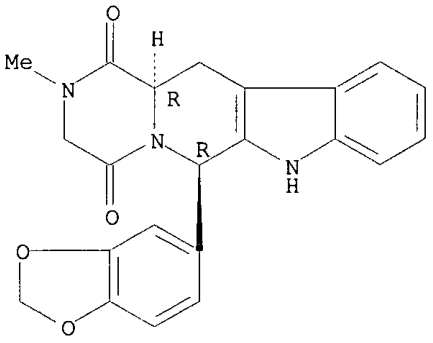
AB .beta.-Carboline formulations contain a c-GMP phosphodiesterase inhibitor, a water-sol. diluent, a lubricant, a hydrophilic binder, a disintegrant, and optional microcryst. cellulose and/or a wetting agent, are useful for treating sexual dysfunction. Thus, a tablet formulation contained a .beta.-carboline 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:

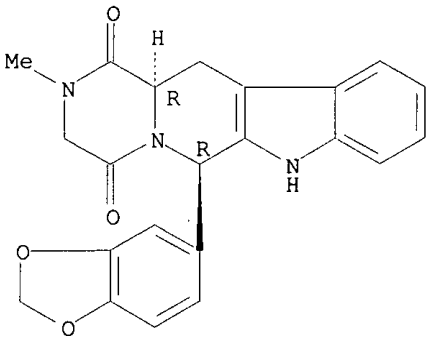
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19931206	A1	20010111	DE 1999-19931206	19990707

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

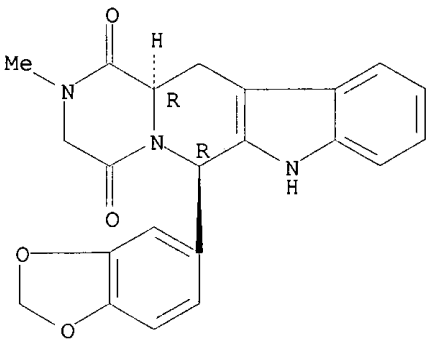
AB A method of treating female arousal disorder in a female patient is disclosed. The method includes orally administering an agent that inhibits cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase type 5 to the female patient.

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)

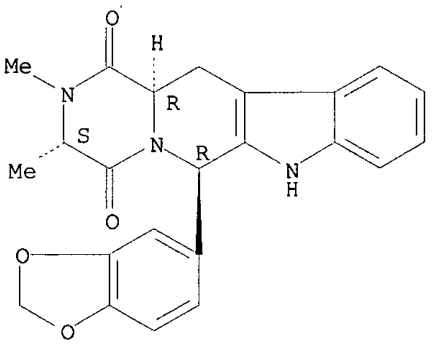
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

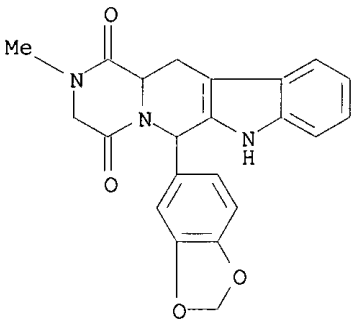


RN 171596-40-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

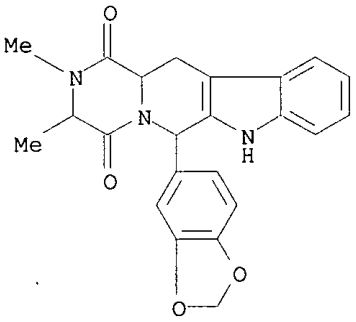
Absolute stereochemistry. Rotation (+).



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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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 6025494 A 20000215 US 1998-133078 19980812
EP 1113800 A1 20010711 EP 1999-945201 19990826
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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
US 1996-669389 A3 19960716
US 1998-133078 A1 19980812
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WO 1999-US19466 W 19990826
OTHER SOURCE(S): MARPAT 133:329627
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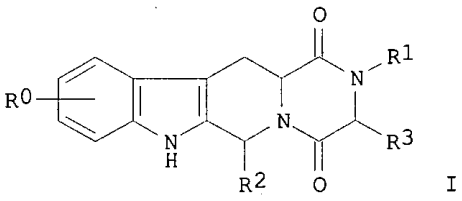

I

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
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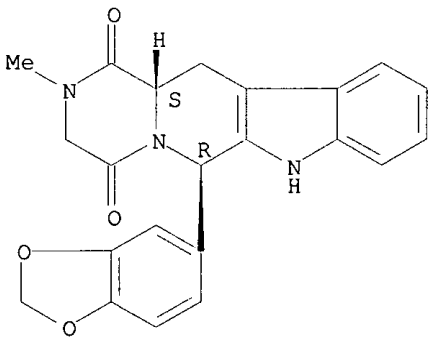
187935-15-5P 303984-32-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tetracyclic cyclic GMP-specific phosphodiesterase inhibitors and their use in disease treatment)

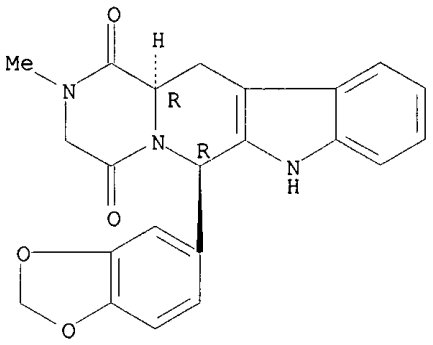
RN 171488-01-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



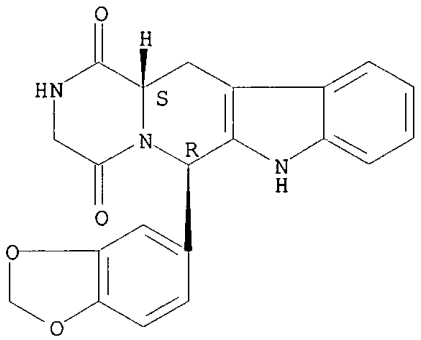
RN 171488-03-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



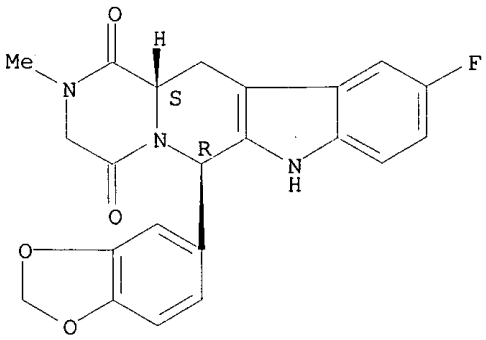
RN 171488-04-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

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)

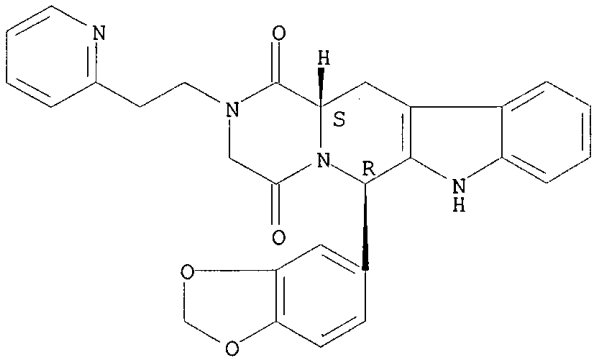
Relative stereochemistry.



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)-

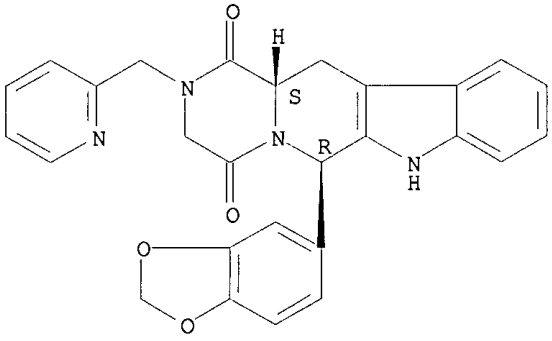
2,3,6,7,12,12a-hexahydro-2-[2-(2-pyridinyl)ethyl]-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



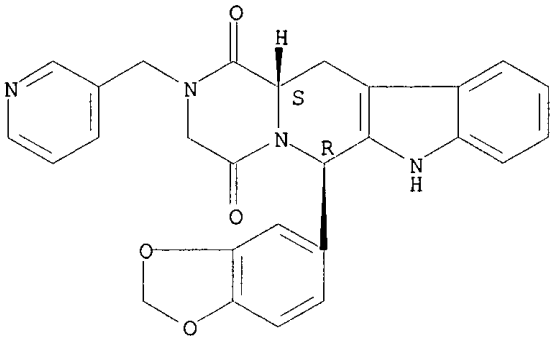
RN 171488-08-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



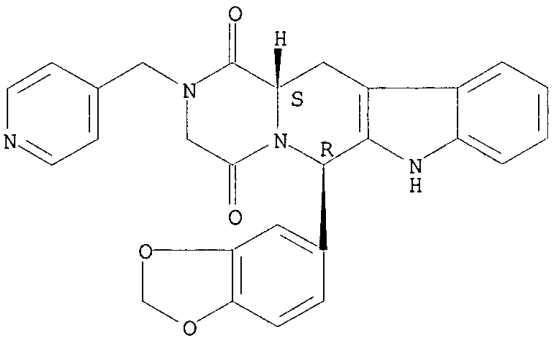
RN 171488-09-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(3-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



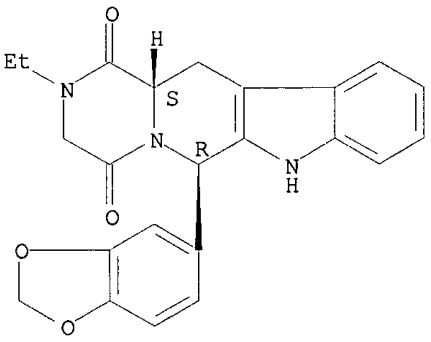
RN 171488-10-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(4-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

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)

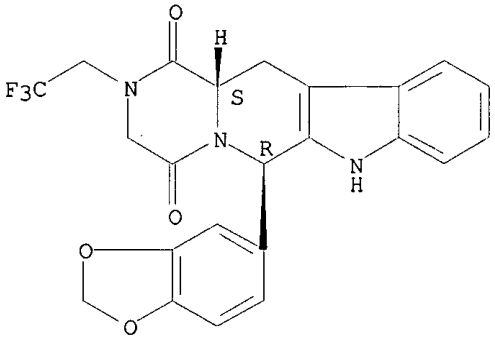
Relative stereochemistry.



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)-

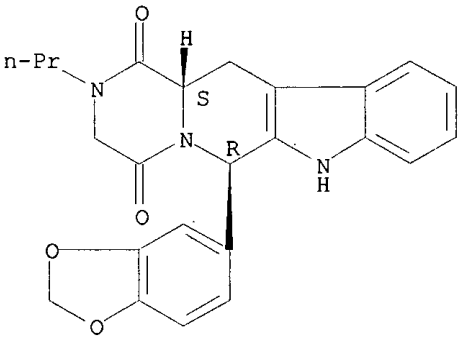
2,3,6,7,12,12a-hexahydro-2-(2,2,2-trifluoroethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



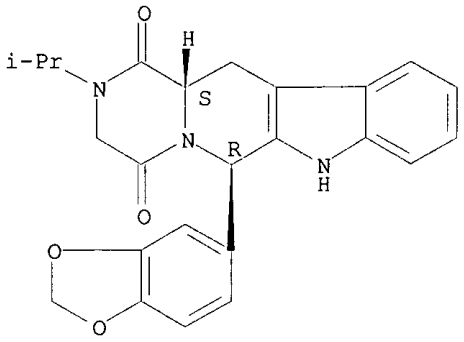
RN 171488-13-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-propyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



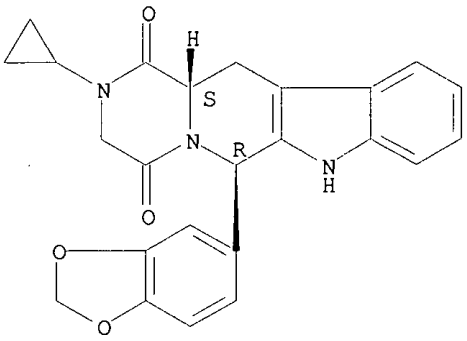
RN 171488-14-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



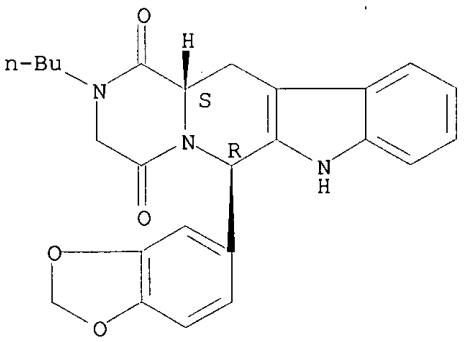
RN 171488-15-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopropyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

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)

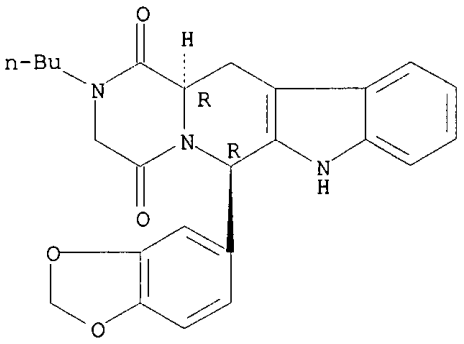
Relative stereochemistry.



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)-

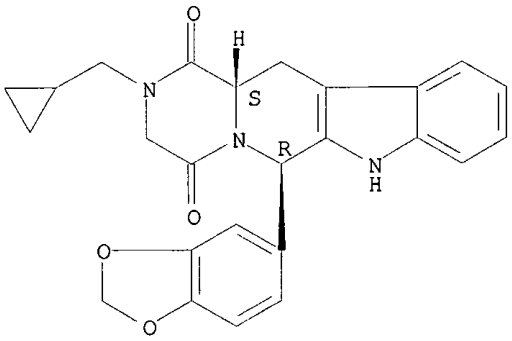
2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



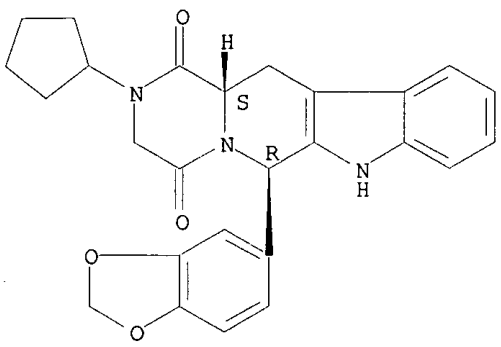
RN 171488-18-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclopropylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



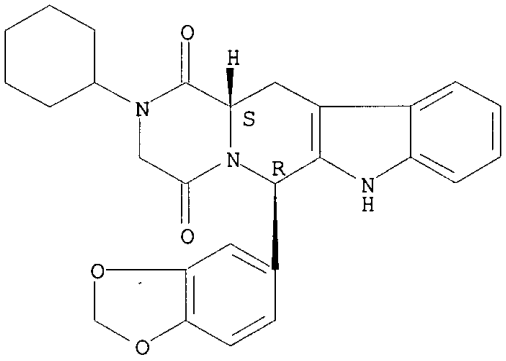
RN 171488-19-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



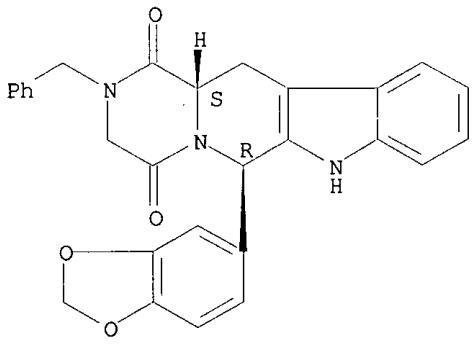
RN 171488-20-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclohexyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-21-4 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-(phenylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



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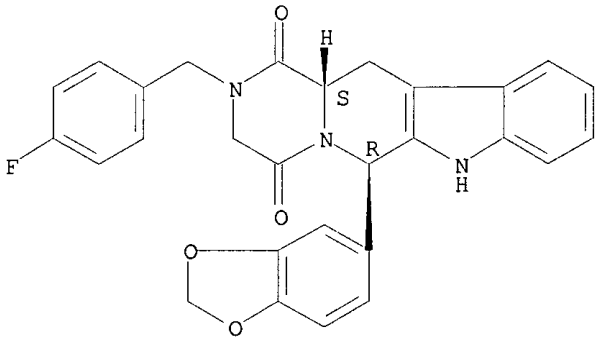
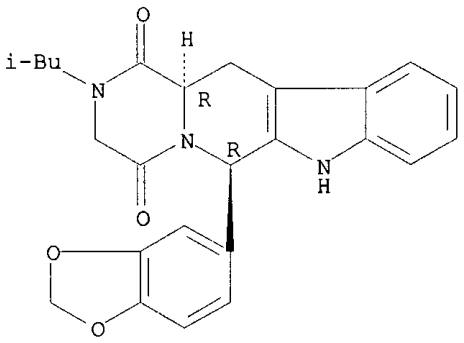
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(4-fluorophenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



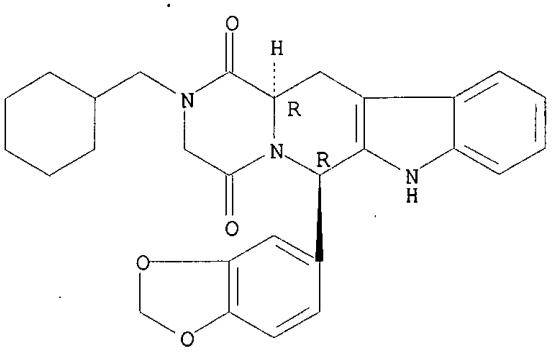
RN 171488-76-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-methylpropyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



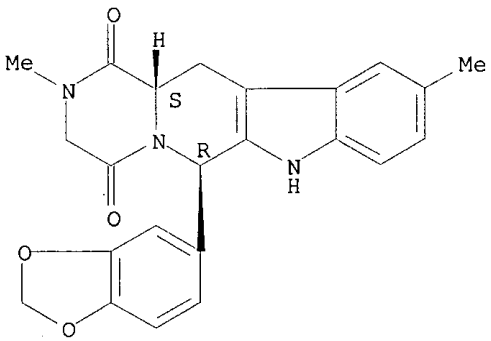
RN 171488-77-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclohexylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



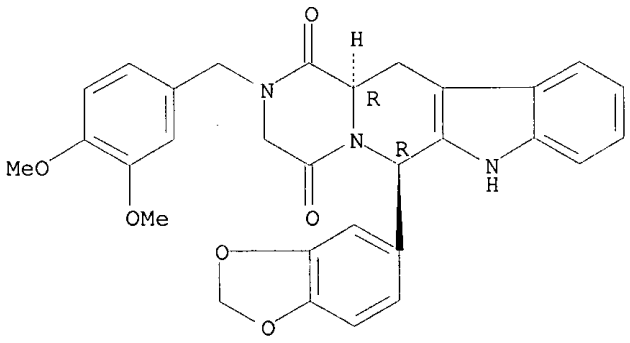
RN 171488-86-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,10-dimethyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-87-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(3,4-dimethoxyphenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

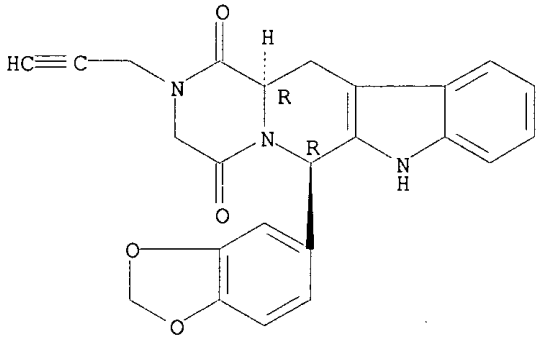
Absolute stereochemistry. Rotation (+).



RN 171488-91-8 CAPLUS

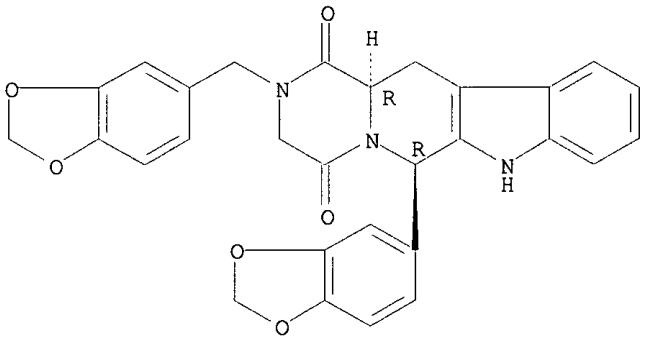
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-propynyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



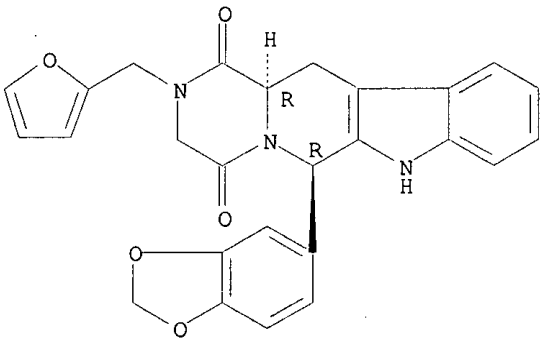
RN 171488-92-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(1,3-benzodioxol-5-ylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



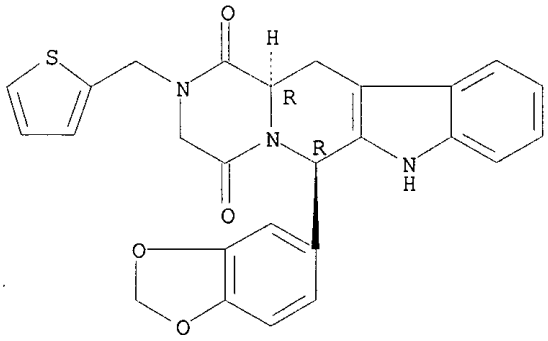
RN 171488-94-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(2-furanylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



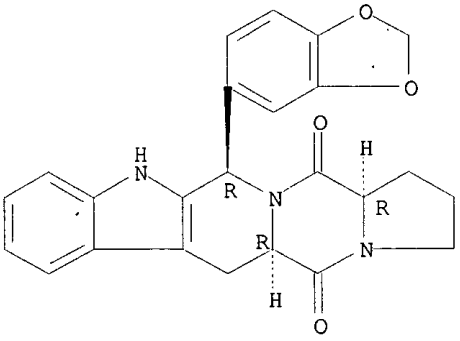
RN 171488-95-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-thienylmethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171489-01-3 CAPLUS
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

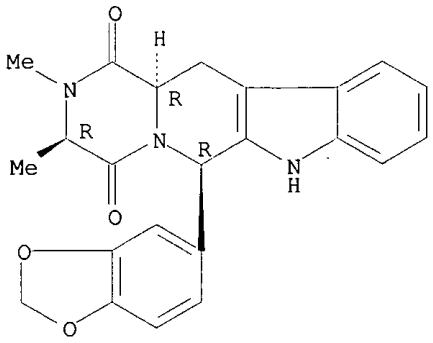


RN 171489-02-4 CAPLUS

Prepared by Toby Port, STIC, Biotech Library 308-3534

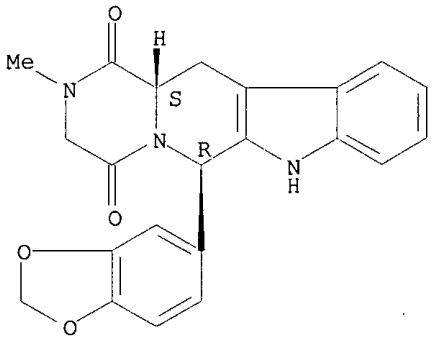
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3R,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



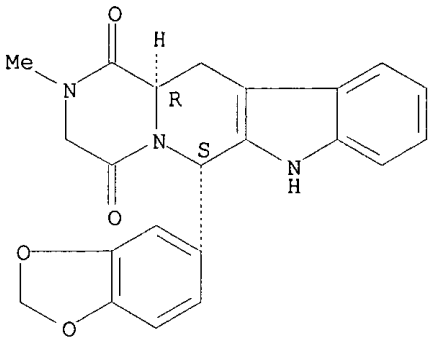
RN 171596-27-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



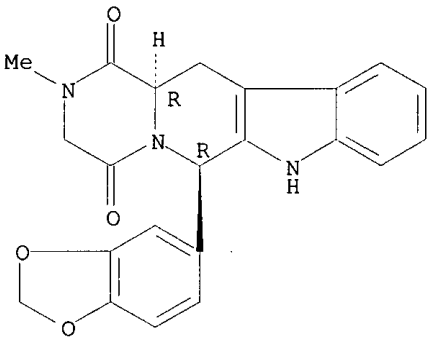
RN 171596-28-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6S,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



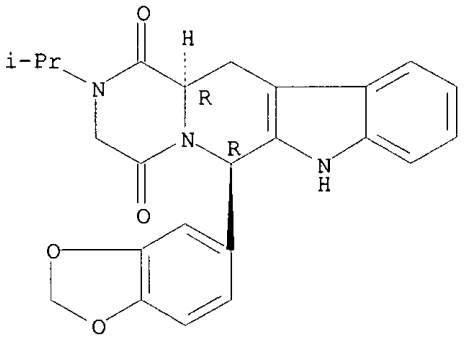
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-30-8 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-(1-methylethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

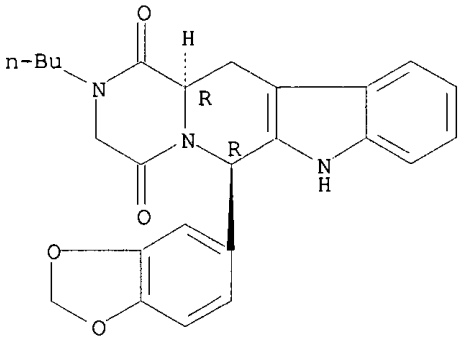
Absolute stereochemistry. Rotation (+).



RN 171596-31-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-

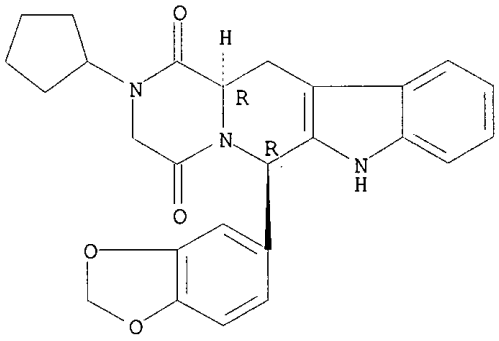
2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



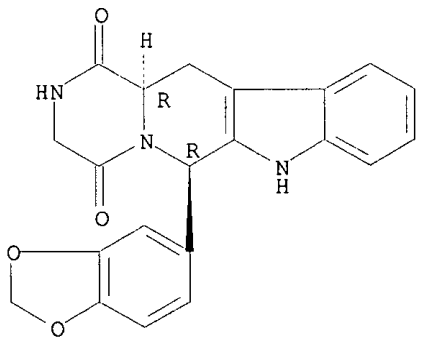
RN 171596-32-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



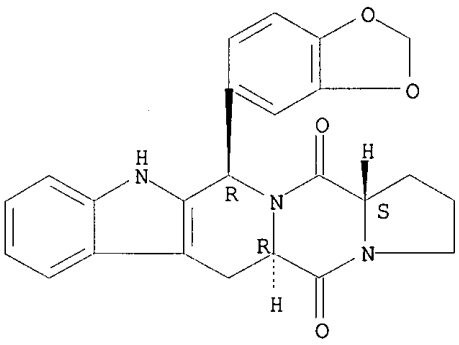
RN 171596-36-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



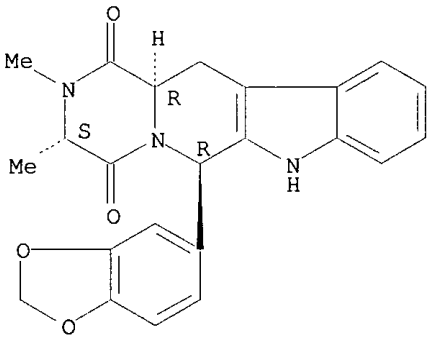
RN 171596-39-7 CAPLUS
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



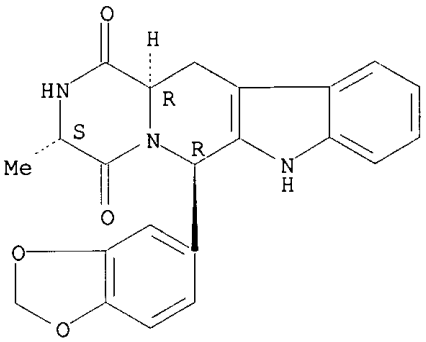
RN 171596-40-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



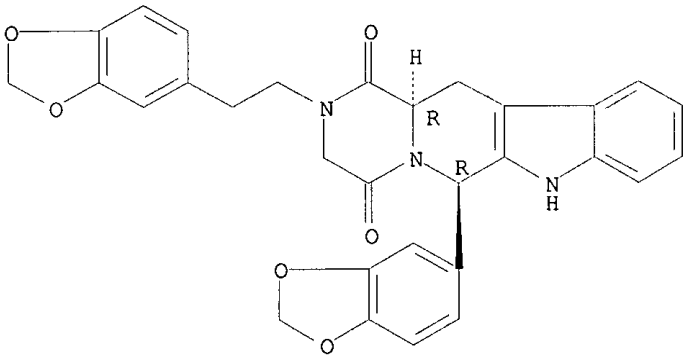
RN 187935-15-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-methyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303984-32-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-(1,3-benzodioxol-5-yl)ethyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 27 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:686171 CAPLUS
DOCUMENT NUMBER: 133:271672
TITLE: Phosphodiesterase inhibitor preparation for treatment of sexual functional disorders
PATENT ASSIGNEE(S): Lilly Icos Llc, USA
SOURCE: Ger. Gebrauchsmusterschrift, 47 pp.
CODEN: GGXXFR
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

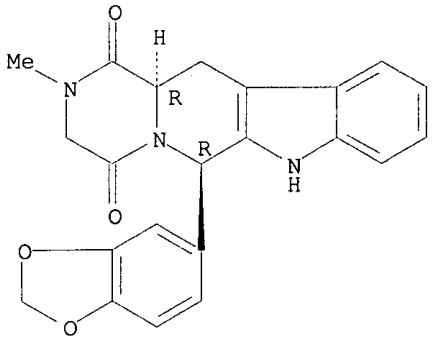
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 20007861	U1	20000928	DE 2000-20007861	20000426
NO 2000002097	A	20011026	NO 2000-2097	20000425
CA 2307101	AA	20001030	CA 2000-2307101	20000426
FI 2000000976	A	20001030	FI 2000-976	20000426

NL 1015027 A1 20001031 NL 2000-1015027 20000426
NL 1015027 C2 20010214
SE 2000001518 A 20001031 SE 2000-1518 20000426
ZA 2000002058 A 20001102 ZA 2000-2058 20000426
WO 2000066099 A2 20001109 WO 2000-US11129 20000426
WO 2000066099 A3 20010118
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
DE 10021266 A1 20001116 DE 2000-10021266 20000426
JP 2000336043 A2 20001205 JP 2000-126472 20000426
FR 2795646 A1 20010105 FR 2000-5296 20000426
GB 2351663 A1 20010110 GB 2000-10199 20000426
LT 4758 B 20010226 LT 2000-35 20000426
LV 12560 B 20010420 LV 2000-56 20000426
CN 1292264 A 20010425 CN 2000-106987 20000426
BE 1012957 A5 20010605 BE 2000-295 20000426
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
LU 90569 A2 20020227 LU 2000-90569 20000426
NO 2001005275 A 20011206 NO 2001-5275 20011029
PRIORITY APPLN. INFO.: US 1999-132036P P 19990430
WO 2000-US11129 W 20000426

AB A formulation for the treatment of sexual malfunctions (e.g., erectile dysfunction in men and decreased libido in women) which contains a phosphodiesterase 5 inhibitor with a IC50 of at least 100-fold lower than that with phosphodiesterase 6 as active ingredient, and which inhibits phosphodiesterase 5 with an IC50 of at least 1000-fold lower than for phosphodiesterase 1c and a IC50 for PDE5 of below 10 nM.

IT **171596-29-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(phosphodiesterase inhibitor prepn. for treatment of sexual functional 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 28 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:666601 CAPLUS
DOCUMENT NUMBER: 133:256811
TITLE: Pharmaceutical compositions containing dopamine agonists in combination with nitric oxide donors for treating and/or preventing sexual dysfunctions
INVENTOR(S): Garvey, David S.
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054773	A1	20000921	WO 2000-US3709	20000310

W: AE, 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

PRIORITY APPLN. INFO.: US 1999-123920P P 19990312
OTHER SOURCE(S): MARPAT 133:256811

AB The present invention is directed to novel compns. comprising at least one dopamine agonist in combination with at least one nitric oxide donor (i.e. compds. that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide synthase). The novel compns. may optionally comprise at least one therapeutic agent, such as, a vasoactive agent, an antiemetic agent, and mixts. thereof. The dopamine agonist is preferably apomorphine. The present invention is also directed to methods for treating and/or preventing sexual dysfunctions and/or enhancing sexual responses in patients. In other embodiments, the present invention is directed to methods treating or preventing neurodegenerative diseases, mitochondrial diseases, spinal cord injury, central or psychostimulant addiction, senile dementia, circulatory disorders, cardiovascular disorders, hyperprolactinemia or myopia. The compds. and/or compns. of the present invention can also be provided in

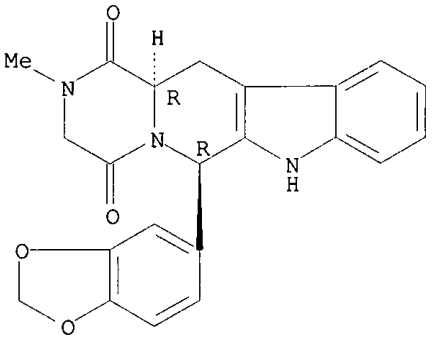
the form of a pharmaceutical kit (no data).

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)
(pharmaceutical compns. contg. dopamine agonists in combination with nitric oxide donors for treating and/or preventing sexual dysfunctions)

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 29 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:645819 CAPLUS
DOCUMENT NUMBER: 133:227820
TITLE: Pharmaceutical compositions for treating erectile dysfunction containing a melanocortin receptor agonist and a cyclic-GMP-specific phosphodiesterase inhibitor or an .alpha.-adrenergic receptor antagonist
INVENTOR(S): Stoner, Elizabeth
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Waldstreicher, Joanne
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 2000053148	A2	20000914	WO 2000-US5711	20000303
WO 2000053148	A3	20001214		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, 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, 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 1161255	A2	20011212	EP 2000-916081	20000303

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 1999-123244P P 19990308
WO 2000-US5711 W 20000303

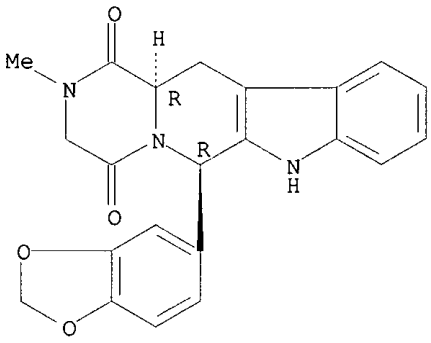
AB The present invention provides for a method for the treatment of erectile dysfunction in a male or female human subject in need of such treatment comprising administration of a therapeutically effective amt. of an agonist of the melanocortin receptor in combination with a therapeutically effective amt. of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. Further, the present invention provides for pharmaceutical compns. useful in the methods of the present invention, as well as a method of manuf. of a medicament useful for treating erectile dysfunction. Effect of the combination of 20 mg/kg of the invention compds. was tested in rats. A hard gelatin capsule contained a melanocortin receptor agonist 5, and a type V phosphodiesterase inhibitor 10 mg.

IT **171596-29-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for treating erectile dysfunction contg. melanocortin receptor agonist and cyclic-GMP-specific phosphodiesterase inhibitor or .alpha.-adrenergic receptor antagonist)

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)

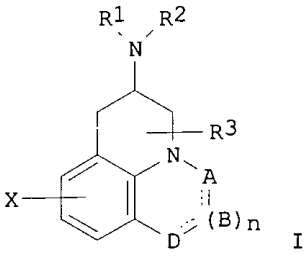
Absolute stereochemistry. Rotation (+).



L12 ANSWER 30 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:475525 CAPLUS
DOCUMENT NUMBER: 133:109946
TITLE: Methylaminodihydroimidazoquinolinones for treating sexual disturbances and inducing mating in animals
INVENTOR(S): Meglasson, Martin Durham; McCall, Robert B.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000040226 A2 20000713 WO 1999-US27951 19991220
WO 2000040226 A3 20010201
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, 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 9916759 A 20010925 BR 1999-16759 19991220
EP 1140092 A2 20011010 EP 1999-967142 19991220
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 1999-114840P P 19990106
US 1999-115051P P 19990108
US 1999-115922P P 19990114
US 1999-120543P P 19990217
WO 1999-US27951 W 19991220
OTHER SOURCE(S): MARPAT 133:109946
GI



I

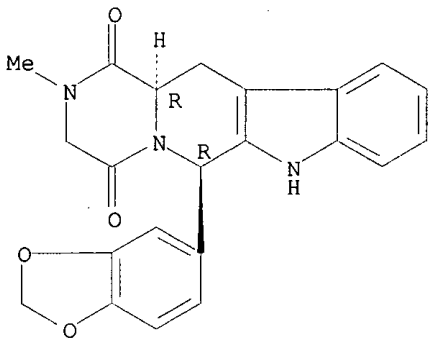
AB The present invention is a method of treating sexual disturbances in humans and inducing mating in non-human mammals using the compds. of formula (I: R1,R2,R3 = H, alkyl, alkenyl, cycloalkyl, etc.; X = H, alkyl, halogen, OH, etc.; A,B,D = CH, CH2, CO, N, etc.; n = 0 or 1) in a dosage range where the sexually therapeutic amt. is from about 0.2 through 8 mg/person/dose and where the sexually mating amt. is from about 0.003 through 0.2 mg/kg/dose.

IT **171596-29-5**, ICOS 351
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(treating sexual disturbances and inducing mating in animals)

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)

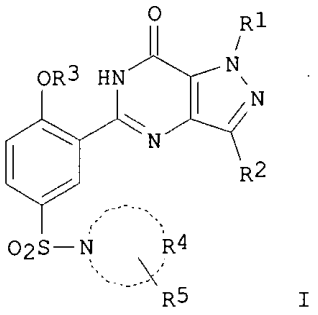
Absolute stereochemistry. Rotation (+).



L12 ANSWER 31 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:392967 CAPLUS
DOCUMENT NUMBER: 133:22405
TITLE: Preventives containing 1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one derivatives and related compounds for nitric acid-induced tolerance
INVENTOR(S): Ellis, Peter
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: Jpn. Kokai Tokkyo Koho, 31 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000159672	A2	20000613	JP 1999-337606	19991129
US 6225315	B1	20010501	US 1999-442821	19991118
EP 1022026	A2	20000726	EP 1999-309406	19991125
EP 1022026	A3	20020410		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 9961788	A1	20000601	AU 1999-61788	19991130
KR 2000035774	A	20000626	KR 1999-53785	19991130

PRIORITY APPLN. INFO.: US 1998-110335P P 19981130
OTHER SOURCE(S): MARPAT 133:22405
GI



I

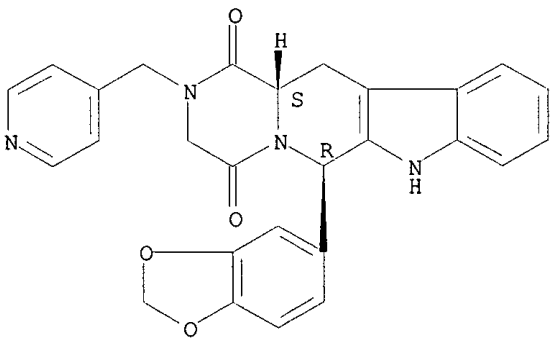
AB The title compds. [I; R1 = H, C1-3 alkyl, C3-5 cycloalkyl, C1-3 perfluoroalkyl; R2 = H, C1-3 perfluoroalkyl, C1-6 alkyl substituted by OH, C1-3 alkoxy, or C3-6 cycloalkyl; R3 = C1-6 alkyl, C3-6 alkenyl, C3-6 alkynyl, C3-7 cycloalkyl, C1-6 perfluoroalkyl, C3-6 cycloalkyl-C1-6 alkyl; R4 together with the R4-bonded N completes 4-N-R6-piperazinyl; R5 = H, C1-4 alkyl, C1-3 alkoxy, NR7R8, CONR7R8; wherein R6 = H, C1-6 alkyl, hydroxy-C2-6 alkyl, R7R8N-C2-6 alkyl, R7R8NCO-C1-6 alkyl, CONR7R8, CSNR7R8, C(:NH)NR7R8; wherein R7, R8 = H, C1-4 alkyl, C1-3 alkoxy-C2-4 alkyl, hydroxy-C2-4 alkyl], pharmacol. acceptable salts, prodrugs, polymorphs, hydrates, solvates, active metabolites, or stereoisomers thereof , which are cGMP phosphodiesterase inhibitors and useful for the prevention of nitrate tolerance (no data), are prepd. The title compds. also include pyrazolo[3,4-d]pyrimidin-4-one, quinazolin-4-one, purin-6-one, pyrido[3,2-d]pyrimidin-4-one, and pyrazino[1',2':1,6]pyrido[3,4-b]indole derivs.

IT **171488-10-1P 171488-15-6P 171596-29-5P 171596-30-8P 171596-32-0P 171596-36-4P 171596-40-0P 187935-15-5P 273207-76-4P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preventives contg. 1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one derivs. and related compds. as cGMP phosphodiesterase inhibitors for nitric acid-induced tolerance)

RN 171488-10-1 CAPLUS

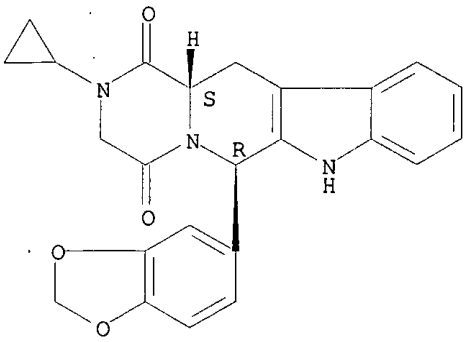
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(4-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



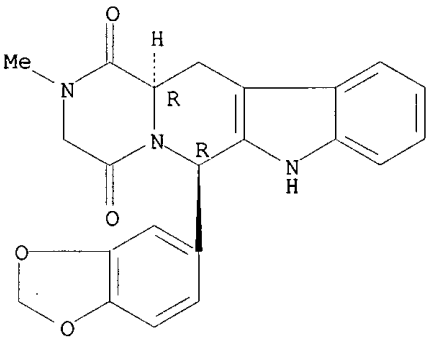
RN 171488-15-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopropyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



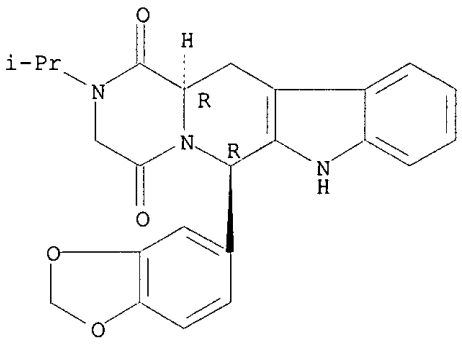
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



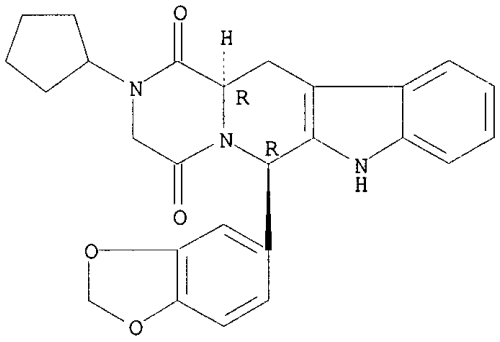
RN 171596-30-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



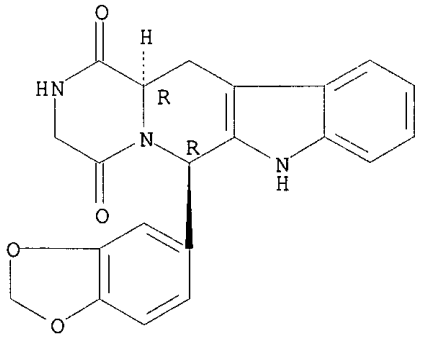
RN 171596-32-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-36-4 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-, (6R,12aR)- (9CI) (CA INDEX NAME)

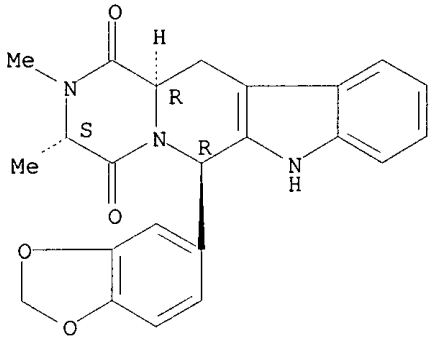
Absolute stereochemistry. Rotation (+).



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

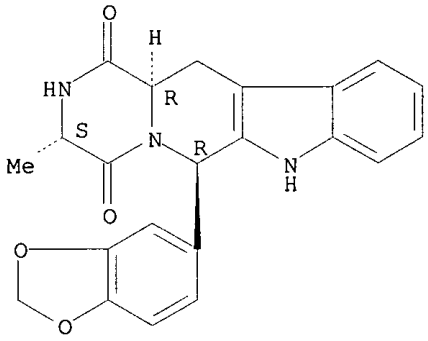
NAME)

Absolute stereochemistry. Rotation (+).



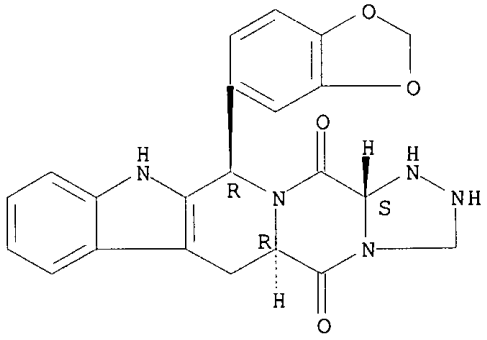
RN 187935-15-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-methyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 273207-76-4 CAPLUS
CN 5H,14H-1,2,4-Triazolo[4'',3'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

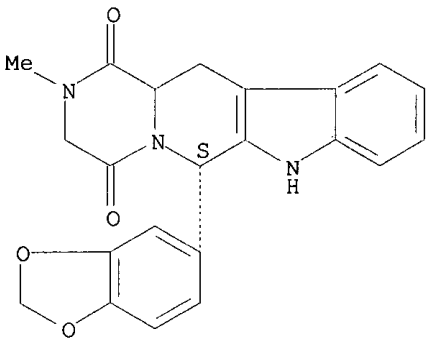


L12 ANSWER 32 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:240994 CAPLUS
DOCUMENT NUMBER: 132:270098
TITLE: Tablets immediately disintegrating in the oral cavity
INVENTOR(S): Furitsu, Hisao; Kato, Akira; Ohwaki, Takayuki; Yasui, Masanori
PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020033	A1	20000413	WO 1999-JP5298	19990928
W: CA, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1120120	A1	20010801	EP 1999-944874	19990928
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000178204	A2	20000627	JP 1999-276133	19990929
JP 2000191518	A2	20000711	JP 1999-276134	19990929

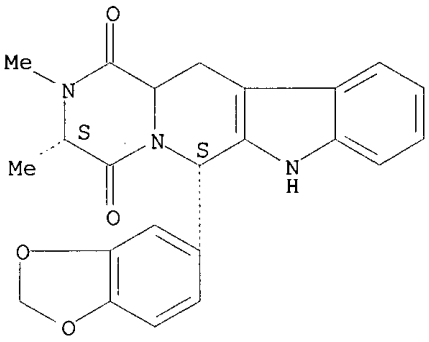
PRIORITY APPLN. INFO.: JP 1998-282378 A 19981005
JP 1998-295947 A 19981019
WO 1999-JP5298 W 19990928
OTHER SOURCE(S): MARPAT 132:270098
AB The invention relates to tablets immediately disintegrating in the oral cavity which contain a phosphodiesterase inhibitor having an effect of ameliorating erectile dysfunction and a process for producing the same; and tablets immediately disintegrating in the oral cavity which contain a hardly sol. drug and show an improved soly.; and a process for producing the same. Namely, tablets immediately disintegrating in the oral cavity which contain a cyclic GMP phosphodiesterase inhibitor [e.g. sildenafil] and saccharides and process for producing the same; and a process for producing tablets immediately disintegrating in the oral cavity which comprises dissolving the hardly sol. drug together with a surfactant and/or a water-sol. polymer in an org. solvent or an aq. org. solvent, mixing saccharides with a molded matter obtained by coating a filler or granulating together with a filler, adding an org. solvent, water or an aq. org. solvent thereto, kneading the resultant mixt. and then compression molding the same.
IT **263392-02-5 263392-03-6**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tablets immediately disintegrating in the oral cavity)
RN 263392-02-5 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-, (6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 263392-03-6 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-2,3-dimethyl-, (3S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 33 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:753072 CAPLUS
DOCUMENT NUMBER: 131:346565
TITLE: Combination of phentolamine and cyclic GMP phosphodiesterase inhibitors for the treatment of sexual dysfunction
INVENTOR(S): Estok, Thomas Mark
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9959584	A1	19991125	WO 1999-US7046	19990517

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT,

RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, 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

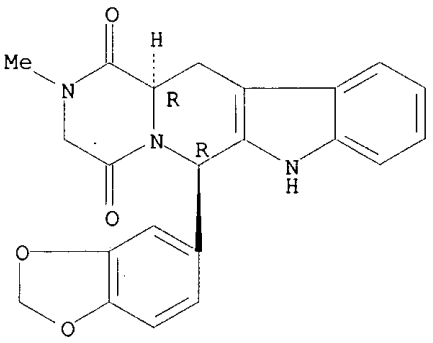
AU 9940685 A1 19991206 AU 1999-40685 19990517
PRIORITY APPLN. INFO.: US 1998-81640 A 19980520
US 1998-82977 A2 19980521
US 1998-106517 A 19980629
WO 1999-US7046 W 19990517

AB A method of treating sexual dysfunction comprising administering a therapeutically effective amt. of a combination of phentolamine and cGMP PDE inhibitor (e.g. sildenafil), as well as pharmaceutical compns. and kits useful in those methods, are disclosed.

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)
(phentolamine and cyclic GMP phosphodiesterase inhibitors for the treatment of sexual dysfunction)

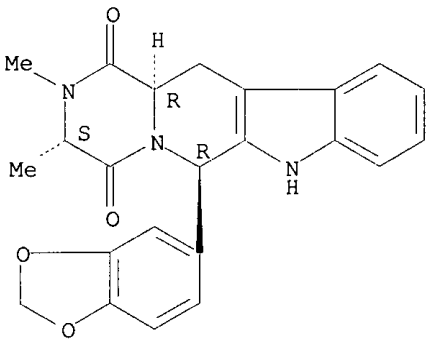
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



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 (+).



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

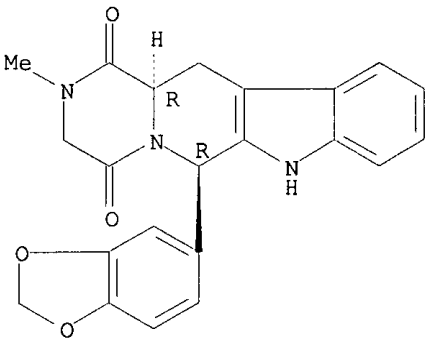
L12 ANSWER 34 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:393867 CAPLUS
DOCUMENT NUMBER: 131:193591
TITLE: IC-351 ICOS Corp
AUTHOR(S): Norman, Peter
CORPORATE SOURCE: Norman Consulting, Bucks, SL1 8JW, UK
SOURCE: Current Opinion in Central & Peripheral Nervous System Investigational Drugs (1999), 1(2), 268-271
CODEN: COCDFA; ISSN: 1464-844X
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 35 refs. IC-351 (GF-196960), an inhibitor of phosphodiesterase 5 (PDE5) from ICOS Corp, is in phase II trials for the treatment of mild to moderate erectile dysfunction (ED) [274568], [296831]. A randomized, placebo-controlled, crossover study assessed the safety and physiol. effects of IC-351 in patients with ED [274568]. Enrollment was completed in Apr. 1998 [284935]. Results from the trial showed that IC-351 demonstrated significant benefit over placebo [311566]. In Oct. 1998, ICOS entered into a joint venture agreement with Eli Lilly for the development and commercialization of IC-351 for the treatment of sexual dysfunction [300118], [310951]. IC-351 is also in development for the treatment of female sexual dysfunction [321995]. In Mar. 1998, the company announced that the compd. was in preclin. evaluation for the treatment of hypertension [284638]. A collaboration with Glaxo Wellcome (GW) was terminated in Mar. 1997 [240438] and intellectual property rights were assigned to ICOS. This left ICOS to develop the compds. with royalties payable to GW. Although GW reserved the right to pursue its own program, it does not appear to be doing so. In Feb. 1999 Deutsche Bank predicted sales of $200 million in 2002 rising to $400 million in 2003 for IC-351 [316821].

IT **171596-29-5**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(effect of IC-351 for treatment of mild to moderate 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 (+).



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 35 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:215760 CAPLUS
DOCUMENT NUMBER: 126:203727
TITLE: Use of cGMP-phosphodiesterase inhibitors to treat impotence
INVENTOR(S): Daugan, Alain Claude-Marie
PATENT ASSIGNEE(S): Laboratoire Glaxo Wellcome S.A., Fr.; Daugan, Alain Claude-Marie
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9703675	A1	19970206	WO 1996-EP3024	19960711
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
CA 2226784	AA	19970206	CA 1996-2226784	19960711
AU 9664191	A1	19970218	AU 1996-64191	19960711
AU 704955	B2	19990513		
EP 839040	A1	19980506	EP 1996-923985	19960711
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CN 1195290	A	19981007	CN 1996-196723	19960711
BR 9609758	A	19990126	BR 1996-9758	19960711
JP 11509221	T2	19990817	JP 1996-506248	19960711
CZ 289686	B6	20020313	CZ 1998-33	19960711
NO 9800153	A	19980310	NO 1998-153	19980113
US 6140329	A	20001031	US 1998-981989	19980310
US 6143746	A	20001107	US 1998-154051	19980916

PRIORITY APPLN. INFO.:
GB 1995-14464 A 19950714
GB 1994-1090 A 19940121
WO 1995-EP183 A2 19950119
GB 1995-14465 A 19950714

WO 1996-EP3024 W 19960711
WO 1996-EP3025 A2 19960711

OTHER SOURCE(S): MARPAT 126:203727

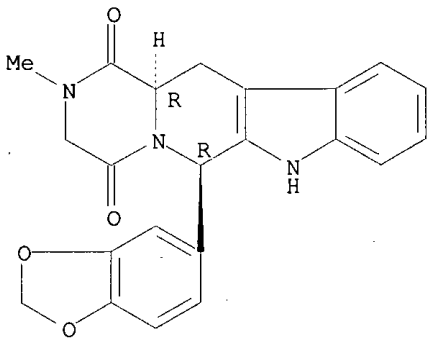
AB Compds. such as (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, (3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, and physiol. acceptable salts and solvates thereof, can be used as cGMP-phosphodiesterase inhibitors in the treatment of impotence.

IT **171596-29-5P 171596-40-0P**
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)
(cGMP-phosphodiesterase inhibitor formulations to treat impotence)

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)

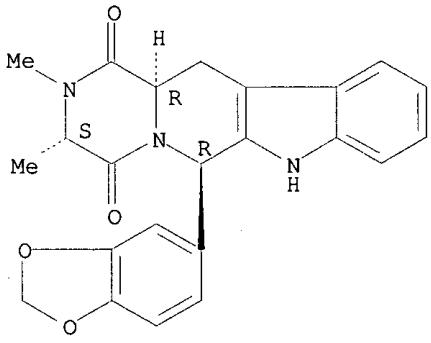
Absolute stereochemistry. Rotation (+).



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)

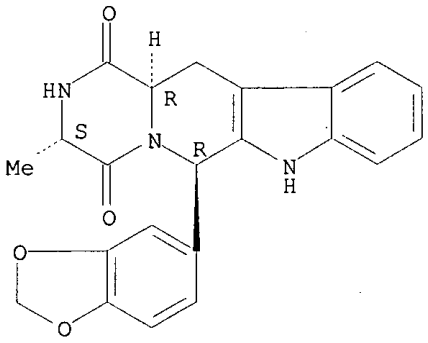
Absolute stereochemistry. Rotation (+).



IT **187935-15-5P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cGMP-phosphodiesterase inhibitor formulations to treat impotence)

RN 187935-15-5 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-methyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 36 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:101617 CAPLUS
DOCUMENT NUMBER: 126:108935
TITLE: Method of producing a solid dispersion of a poorly water-soluble drug
INVENTOR(S): Butler, James Matthew
PATENT ASSIGNEE(S): Glaxo Group Limited, UK; Butler, James Matthew
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9638131	A1	19961205	WO 1996-EP2299	19960530
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
AU 9660026	A1	19961218	AU 1996-60026	19960530
EP 828479	A1	19980318	EP 1996-917457	19960530
EP 828479	B1	20011024		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 207344	E	20011115	AT 1996-917457	19960530
US 5985326	A	19991116	US 1998-952938	19980206

PRIORITY APPLN. INFO.: GB 1995-11220 A 19950602
WO 1996-EP2299 W 19960530

AB A process for prepg. solid dispersions of poorly sol. drugs comprises (1) providing an intimate mixt. contg. the carrier or excipient and a nonaq. water-miscible solvent, and optionally, water, (2) mixing the intimate mixt. with the poorly water-sol. drug, and (3) pptg. the drug and the carrier or excipient. Specifically, solid dispersions 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 (I)

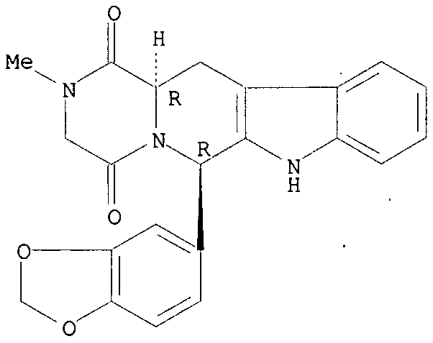
and (+)-N-[1-(adamantanmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl]-N'-phenylurea are described. I 1 g and hydroxypropyl Me cellulose phthalate 1 g were dissolved in a 9:1 mixt. of acetone/water (27 mL) and 0.25 M HCl 83 mL was added to obtain a ppt. The ppt. was filtered, washed with water, dried, and milled. A tablet contg. 100 mg ppt. was formulated.

IT **171596-29-5P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrazinopyridoindole deriv. in manuf. of solid dispersion of poorly water-sol. 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 37 OF 37 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:986316 CAPLUS
DOCUMENT NUMBER: 124:55977
TITLE: Preparation of pyrazinopyridoindolediones as inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase
INVENTOR(S): Daugan, Alain Claude-Marie
PATENT ASSIGNEE(S): Laboratoires Glaxo S.A., Fr.
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
TW 378210	B	20000101	TW 1995-84100415	19950118
CA 2181377	AA	19950727	CA 1995-2181377	19950119
AU 9515748	A1	19950808	AU 1995-15748	19950119

AU 689205	B2	19980326			
ZA 9500424	A	19950927	ZA 1995-424	19950119	
EP 740668	A1	19961106	EP 1995-907565	19950119	
EP 740668	B1	19980729			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
CN 1143963	A	19970226	CN 1995-192078	19950119	
CN 1045777	B	19991020			
HU 74943	A2	19970328	HU 1996-1982	19950119	
JP 09508113	T2	19970819	JP 1995-519339	19950119	
BR 9506559	A	19971028	BR 1995-6559	19950119	
AT 169018	E	19980815	AT 1995-907565	19950119	
IL 112384	A1	19980816	IL 1995-112384	19950119	
ES 2122543	T3	19981216	ES 1995-907565	19950119	
RU 2142463	C1	19991210	RU 1996-117127	19950119	
CZ 286566	B6	20000517	CZ 1996-2116	19950119	
SK 280879	B6	20000814	SK 1996-940	19950119	
PL 179744	B1	20001031	PL 1995-315559	19950119	
LV 11690	B	19970620	LV 1996-228	19960710	
US 5859006	A	19990112	US 1996-669389	19960716	
FI 9602927	A	19960719	FI 1996-2927	19960719	
NO 9603015	A	19960909	NO 1996-3015	19960719	
AU 9873912	A1	19980820	AU 1998-73912	19980626	
AU 707055	B2	19990701			
US 6025494	A	20000215	US 1998-133078	19980812	
US 6143746	A	20001107	US 1998-154051	19980916	
CN 1224720	A	19990804	CN 1998-122779	19981201	
CN 1070492	B	20010905			
US 6127542	A	20001003	US 1999-399667	19990921	

PRIORITY APPLN. INFO.:	GB 1994-1090	A	19940121
	WO 1995-EP183	W	19950119
	GB 1995-14464	A	19950714
	GB 1995-14465	A	19950714
	WO 1996-EP3024	A2	19960711
	WO 1996-EP3025	A2	19960711
	US 1996-669389	A3	19960716
	US 1998-133078	A1	19980812

OTHER SOURCE(S): MARPAT 124:55977

GI For diagram(s), see printed CA Issue.

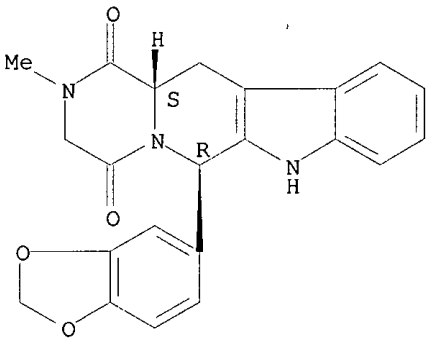
AB The title compds. I [R represents hydrogen, halogen or C1-6 alkyl; R1 represents hydrogen, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, haloC1-6alkyl, C3-8cycloalkyl, etc.; R2 represents an optionally substituted monocyclic arom. ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring Q1 attached to the rest of the mol. via one of the benzene ring carbon atoms and wherein the fused ring A 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; and R3 represents hydrogen or C1-3 alkyl, or R1 and R3 together represent a 3- or 4-membered alkyl or alkenyl chain] are prepd. In an in vitro test for inhibitory effect on cGMP-PDE, 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 (prepn. given) 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
171488-15-6P 171488-16-7P 171488-17-8P
171488-18-9P 171488-19-0P 171488-20-3P
171488-21-4P 171488-22-5P 171488-76-9P
171488-77-0P 171488-86-1P 171488-87-2P
171488-91-8P 171488-92-9P 171488-93-0P

171488-94-1P 171488-95-2P 171489-01-3P
171489-02-4P 171596-27-3P 171596-28-4P
171596-29-5P 171596-30-8P 171596-31-9P
171596-32-0P 171596-36-4P 171596-39-7P
171596-40-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrazinopyridoindolediones as inhibitors of cyclic guanosine monophosphate specific phosphodiesterase)

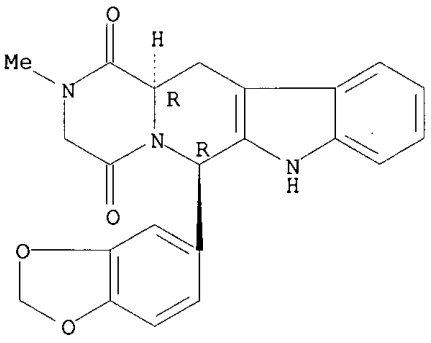
RN 171488-01-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



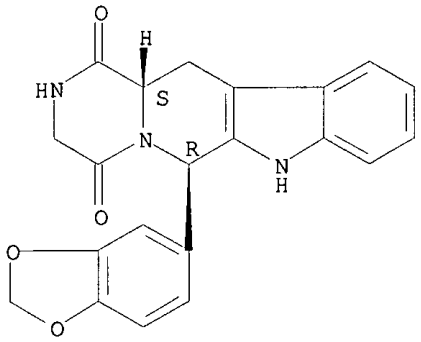
RN 171488-03-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



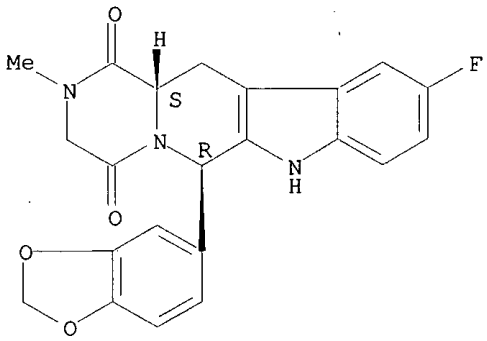
RN 171488-04-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



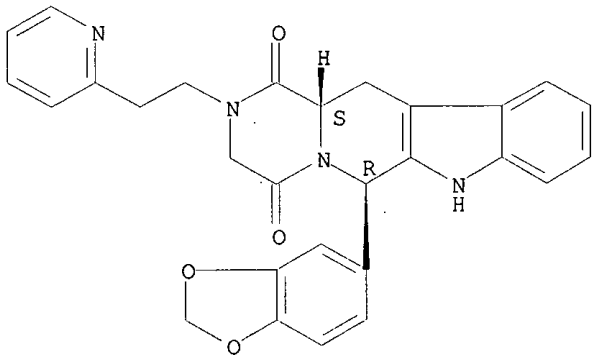
RN 171488-06-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-10-fluoro-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



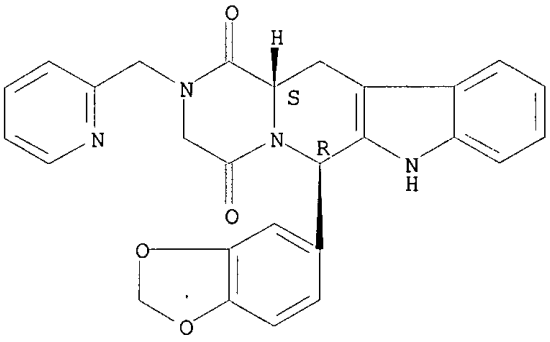
RN 171488-07-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(2-pyridinyl)ethyl]-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



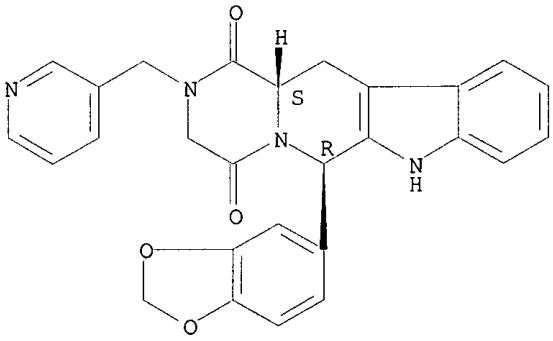
RN 171488-08-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



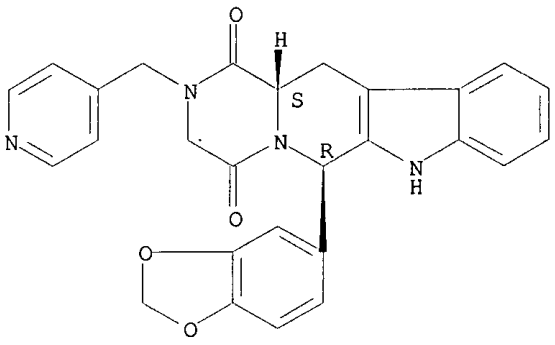
RN 171488-09-8 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(3-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



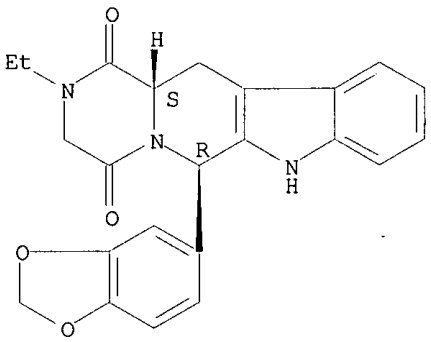
RN 171488-10-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(4-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



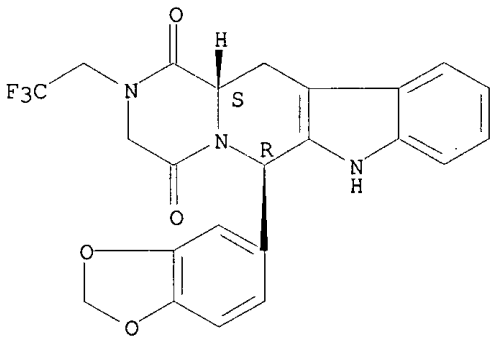
RN 171488-11-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-ethyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

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)

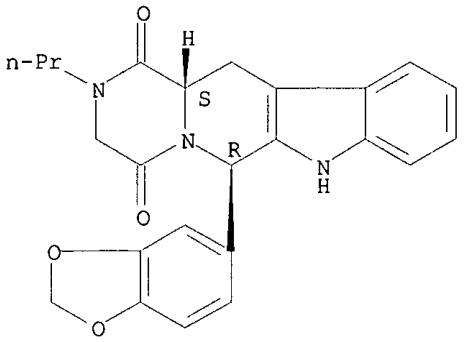
Relative stereochemistry.



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)-

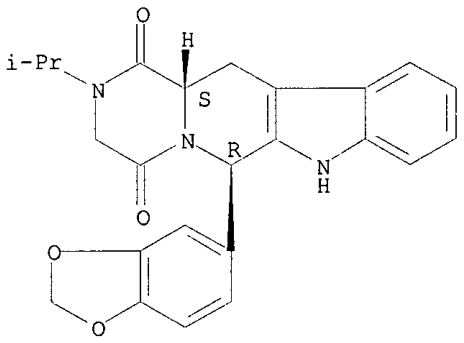
2,3,6,7,12,12a-hexahydro-2-propyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



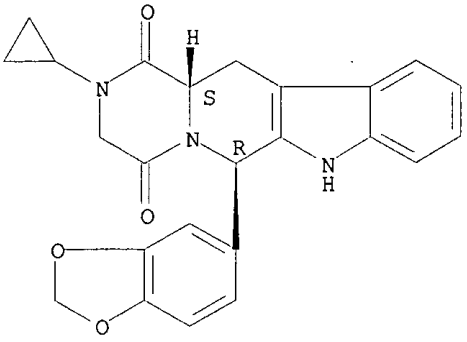
RN 171488-14-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



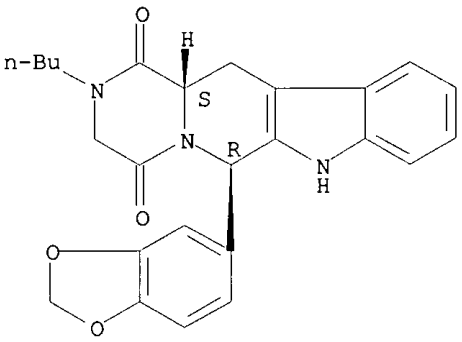
RN 171488-15-6 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopropyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



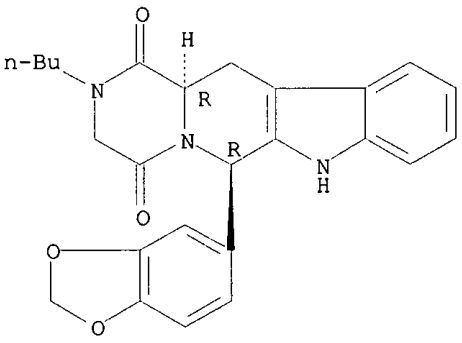
RN 171488-16-7 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

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)

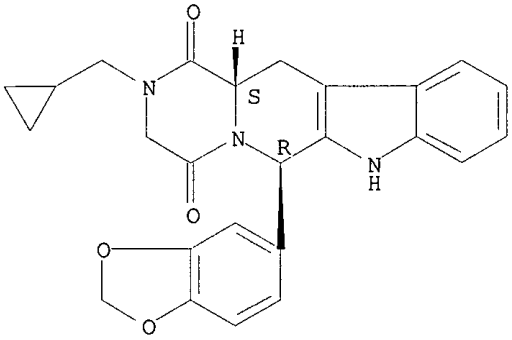
Relative stereochemistry.



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

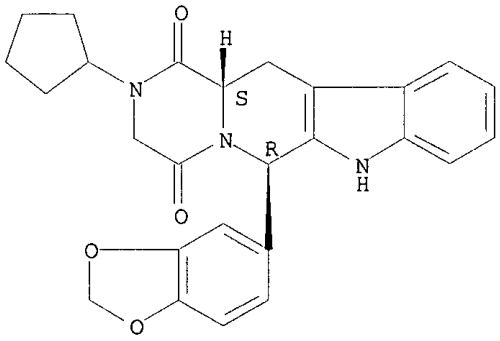
INDEX NAME)

Relative stereochemistry.



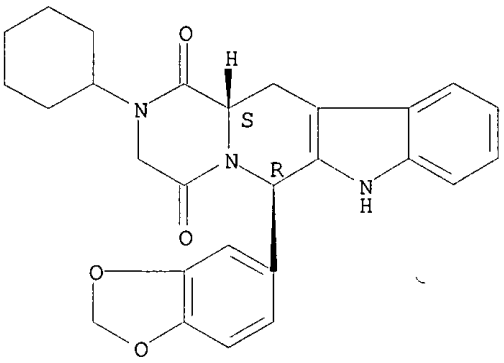
RN 171488-19-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



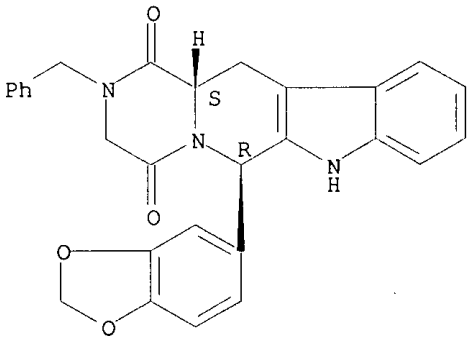
RN 171488-20-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclohexyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



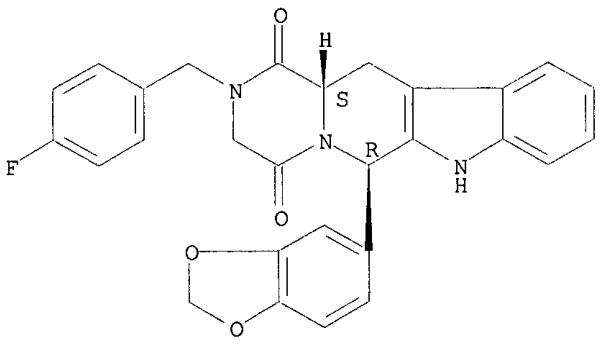
RN 171488-21-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(phenylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



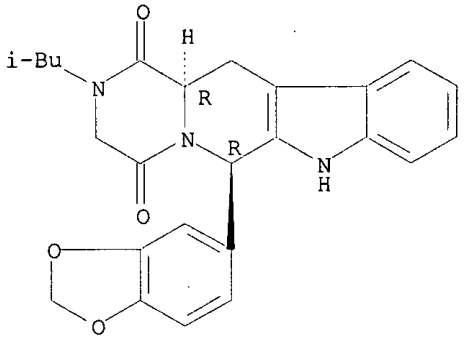
RN 171488-22-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(4-fluorophenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



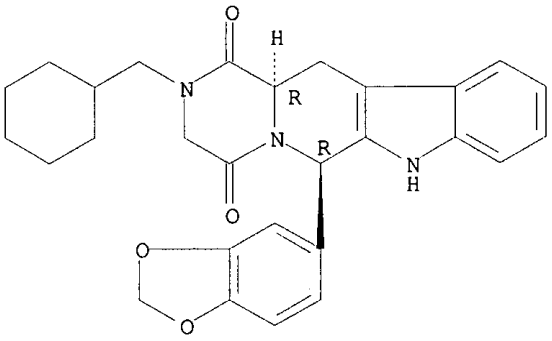
RN 171488-76-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-methylpropyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



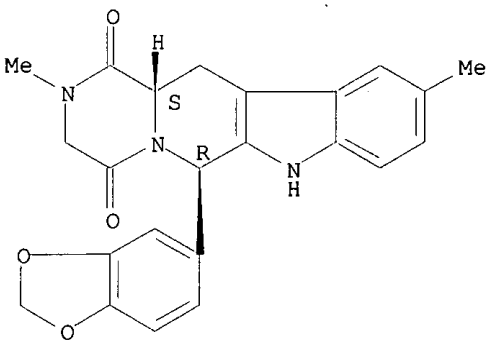
RN 171488-77-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclohexylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



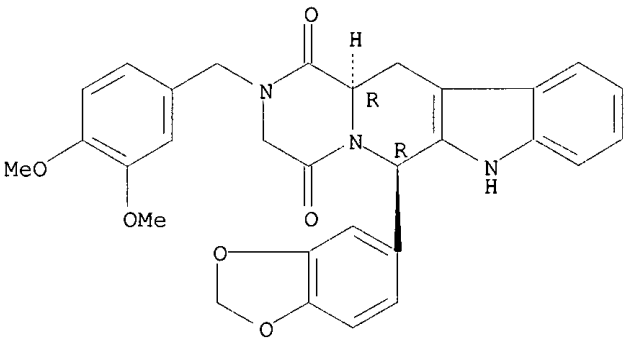
RN 171488-86-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,10-dimethyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



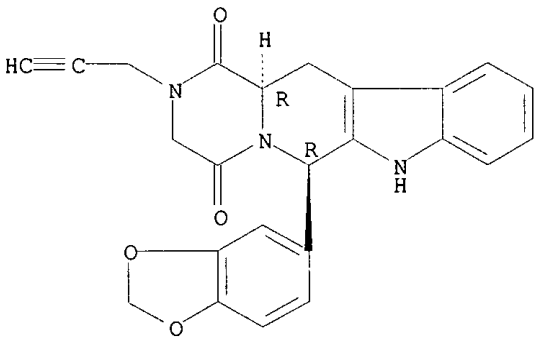
RN 171488-87-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(3,4-dimethoxyphenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171488-91-8 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-propynyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

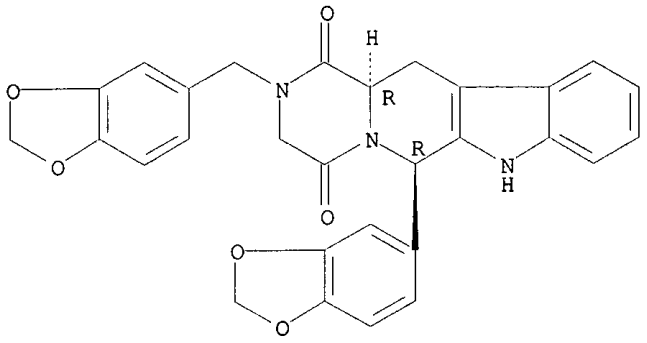
Absolute stereochemistry. Rotation (+).



RN 171488-92-9 CAPLUS

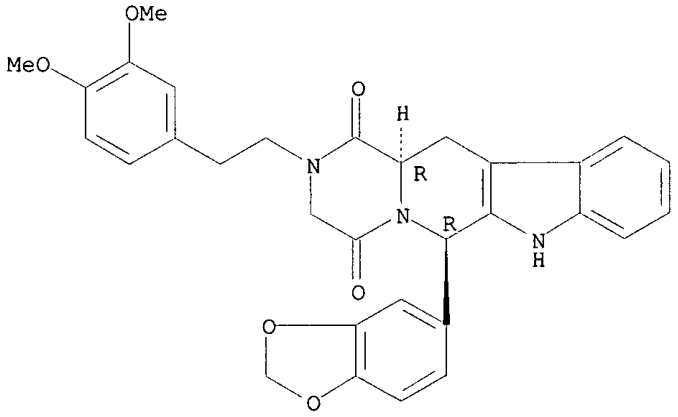
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(1,3-benzodioxol-5-ylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



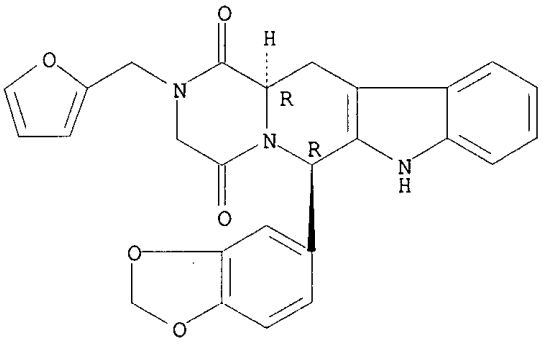
RN 171488-93-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-(3,4-dimethoxyphenyl)ethyl]-2,3,6,7,12,12a-hexahydro-, (6R-trans)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



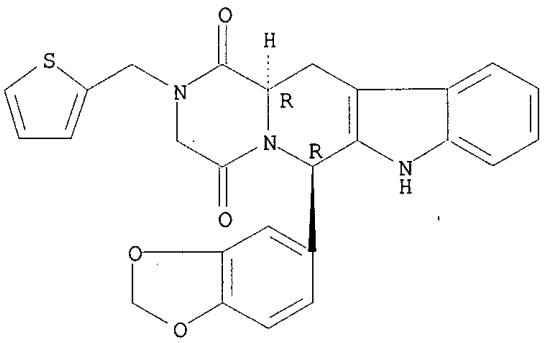
RN 171488-94-1 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(2-furanylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



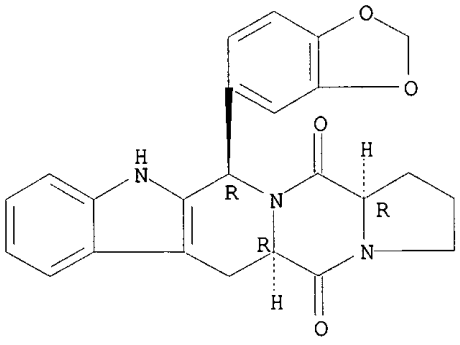
RN 171488-95-2 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-thienylmethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171489-01-3 CAPLUS
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aR)- (9CI) (CA INDEX NAME)

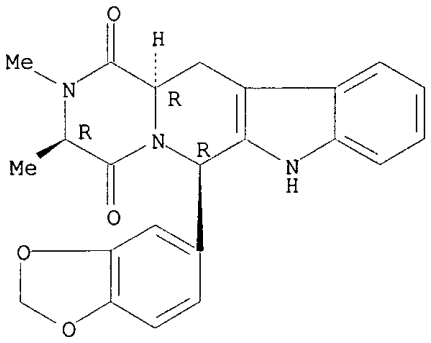
Absolute stereochemistry. Rotation (+).



RN 171489-02-4 CAPLUS

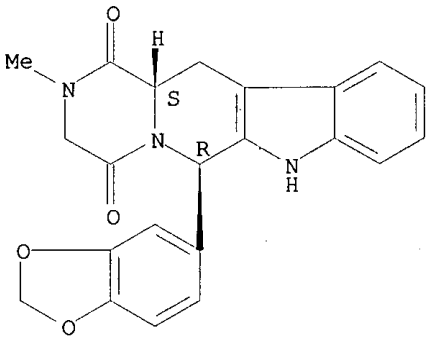
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3R,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



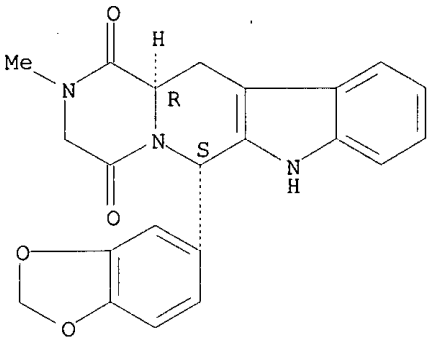
RN 171596-27-3 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



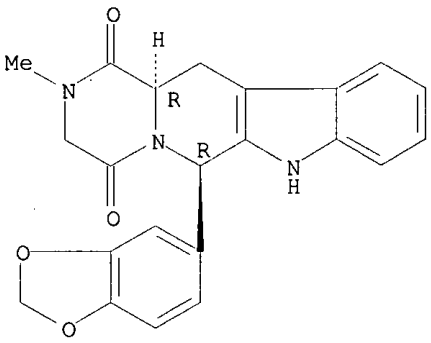
RN 171596-28-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6S,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



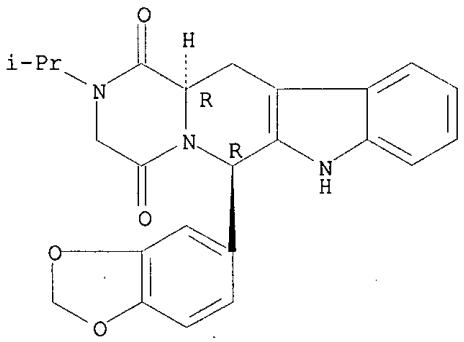
RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-30-8 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-(1-methylethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

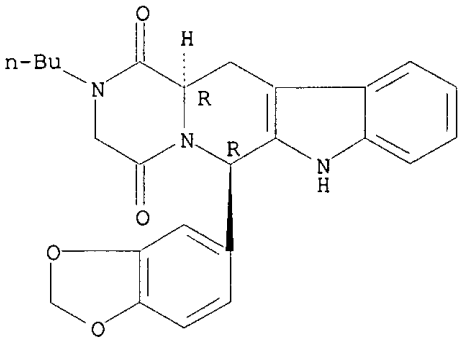
Absolute stereochemistry. Rotation (+).



RN 171596-31-9 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-

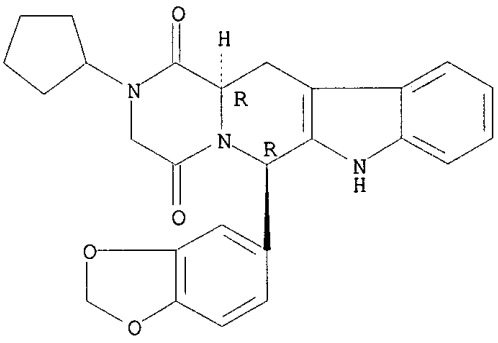
2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



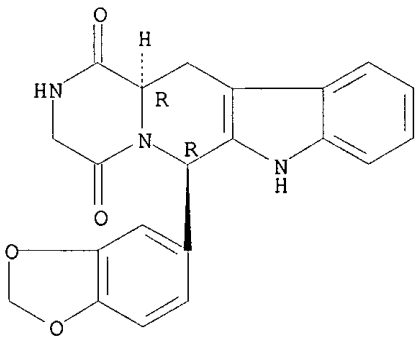
RN 171596-32-0 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



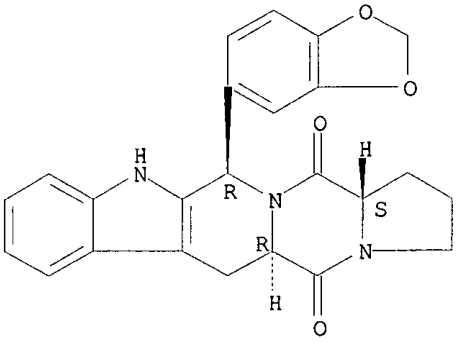
RN 171596-36-4 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



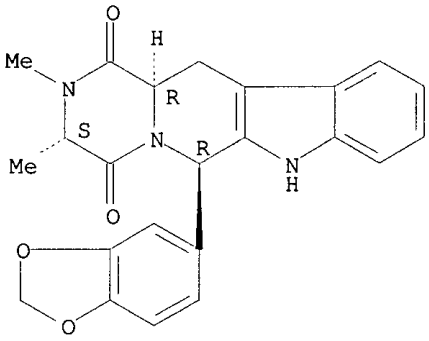
RN 171596-39-7 CAPLUS
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aS)- (9CI) (CA INDEX NAME)

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 (+).



=> file caold; d que nos 116
FILE 'CAOLD' ENTERED AT 14:31:53 ON 16 JUL 2002
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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L8              STR
L10         178 SEA FILE=REGISTRY SSS FUL L8
L16           0 SEA FILE=CAOLD ABB=ON  PLU=ON  L10


=> file home
FILE 'HOME' ENTERED AT 14:31:56 ON 16 JUL 2002
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=> file reg
FILE 'REGISTRY' ENTERED AT 14:02:21 ON 16 JUL 2002
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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
  conducting SmartSELECT searches.

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Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s e1
L3            1 171596-29-5/BI
                (171596-29-5/RN)

=> d ide

L3   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   171596-29-5  REGISTRY
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)
OTHER CA INDEX NAMES:
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-trans)-
OTHER NAMES:
CN   Cialis
CN   GF 196960
CN   IC 351
CN   ICOS 351
CN   Tadalafil
FS   STEREOSEARCH
DR   240822-07-5, 282541-36-0
MF   C22 H19 N3 O4
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, CIN, DRUGNL,
       DRUGPAT, DRUGUPDATES, EMBASE, IPA, PHAR, PROMT, SYNTHLINE, TOXCENTER,
       USPAT2, USPATFULL

Absolute stereochemistry.  Rotation (+).
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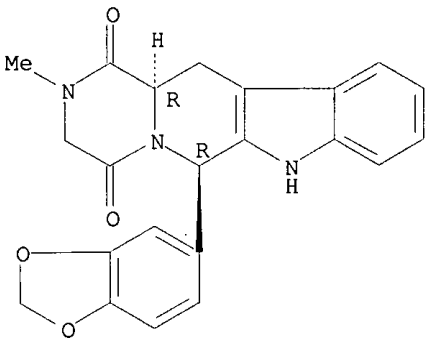


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

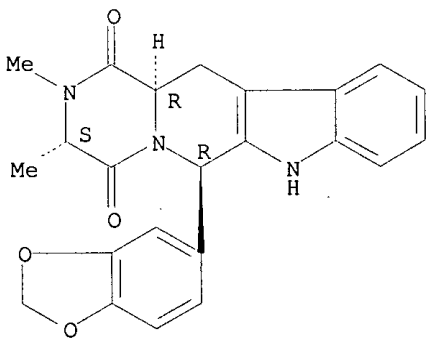
32 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
32 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s e2
L4 1 171596-40-0/BI
(171596-40-0/RN)

=> d ide

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **171596-40-0** REGISTRY
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)
OTHER CA INDEX NAMES:
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-(3.alpha.,6.beta.,12a.alpha.)]-
FS STEREOSEARCH
MF C23 H21 N3 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry. Rotation (+).



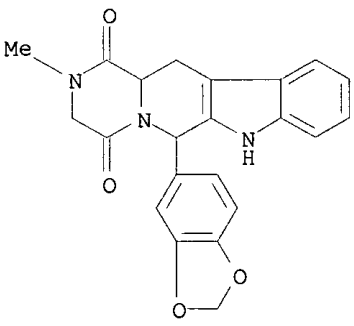
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1967 TO DATE)
8 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s e3
L5 1 304683-09-8/BI
(304683-09-8/RN)

=> d ide

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **304683-09-8** REGISTRY
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)
FS 3D CONCORD
MF C22 H19 N3 O4
SR CA
LC STN Files: CA, CAPLUS, DRUGPAT, DRUGUPDATES



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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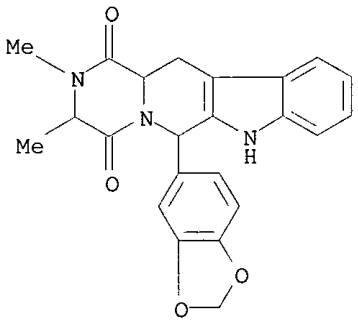
L6 1 304683-11-2/BI
(304683-11-2/RN)

=> d ide

L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **304683-11-2** REGISTRY
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)
FS 3D CONCORD
MF C23 H21 N3 O4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s e5
L7 1 9068-52-4/BI
(9068-52-4/RN)

=> d ide

L7 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **9068-52-4** REGISTRY
CN Phosphodiesterase, guanosine cyclic 3',5'-phosphate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3',5'-cGMP phosphodiesterase
CN 3',5'-Cyclic GMP phosphodiesterase
CN cGMP phosphodiesterase
CN cGMP-binding cGMP-specific phosphodiesterase
CN cGMP-dependent phosphodiesterase
CN cGMP-specific cyclic nucleotide phosphodiesterase
CN cGMP-specific phosphodiesterase
CN Cyclic 3',5'-GMP phosphodiesterase
CN Cyclic GMP phosphodiesterase
CN Cyclic GMP-dependent phosphodiesterase
CN Cyclic guanosine 3',5'-monophosphate phosphodiesterase
CN Cyclic guanosine 3',5'-phosphate phosphodiesterase
CN E.C. 3.1.4.35
CN Guanosine cyclic 3',5'-phosphate phosphodiesterase
CN Guanylate phosphodiesterase
CN Phosphodiesterase 6
CN Phosphodiesterase type 5
CN Phosphodiesterase V
CN Phosphodiesterase VI
CN Photoreceptor phosphodiesterase
CN Type V cGMP-specific phosphodiesterase
CN Type V phosphodiesterase
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CEN, CIN, EMBASE, IFICDB, IFIPAT, IFIUDB, PROMT, TOXCENTER, USPAT2, USPATFULL

Prepared by Toby Port, STIC, Biotech Library 308-3534

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*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
            1856 REFERENCES IN FILE CA (1967 TO DATE)
               7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            1867 REFERENCES IN FILE CAPLUS (1967 TO DATE)


=> file embase; d que l18
FILE 'EMBASE' ENTERED AT 14:58:53 ON 16 JUL 2002
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 FILE COVERS 1974 TO 11 Jul 2002 (20020711/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L17          25 SEA FILE=EMBASE ABB=ON  PLU=ON  TARDANAFIL/CT
L18           9 SEA FILE=EMBASE ABB=ON  PLU=ON  L17/MAJ


=> file wpid; d que l19
FILE 'WPIDS' ENTERED AT 14:59:16 ON 16 JUL 2002
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FILE LAST UPDATED: 11 JUL 2002              <20020711/UP>
MOST RECENT DERWENT UPDATE            200244   <200244/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> The BATCH option for structure searches has been
    enabled in WPINDEX/WPIDS and WPIX  >>>

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY >>>

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
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    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<


L19           9 SEA FILE=WPIDS ABB=ON  PLU=ON  CIALIS OR TADALAFIL OR TARDANAFI
                L OR IC351 OR (IC OR ICOS) (W) 351


=> file biosis; d que l21
FILE 'BIOSIS' ENTERED AT 15:02:48 ON 16 JUL 2002
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 10 July 2002 (20020710/ED)
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L21          16 SEA FILE=BIOSIS ABB=ON  PLU=ON  CIALIS OR IC351 OR (IC OR
                ICOS) (W) (351) OR TADALAFIL OR TARDANAFIL OR GF196960 OR GF
                (W) (196960 OR 196 960)


=> file medline; d que l23
FILE 'MEDLINE' ENTERED AT 15:02:56 ON 16 JUL 2002

 FILE LAST UPDATED: 13 JUL 2002 (20020713/UP).  FILE COVERS 1958 TO DATE.

 On June 9, 2002, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2002 vocabulary.  Enter HELP THESAURUS for details.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.


L23           6 SEA FILE=MEDLINE ABB=ON  PLU=ON  IC351


=> dup rem l12 l23 l19 l21 l23
FILE 'CAPLUS' ENTERED AT 15:04:37 ON 16 JUL 2002
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FILE 'MEDLINE' ENTERED AT 15:04:37 ON 16 JUL 2002

FILE 'WPIDS' ENTERED AT 15:04:37 ON 16 JUL 2002
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FILE 'BIOSIS' ENTERED AT 15:04:37 ON 16 JUL 2002
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PROCESSING COMPLETED FOR L12
PROCESSING COMPLETED FOR L23
PROCESSING COMPLETED FOR L19
PROCESSING COMPLETED FOR L21
L25          58 DUP REM L12 L23 L19 L21 L23 (10 DUPLICATES REMOVED)
                ANSWERS '1-37' FROM FILE CAPLUS  - Answers 1-37 previously displayed in
                ANSWERS '38-43' FROM FILE MEDLINE  structure search
                ANSWER '44' FROM FILE WPIDS
                ANSWERS '45-58' FROM FILE BIOSIS

=> d ibib ab l25 38-58

L25  ANSWER 38 OF 58     MEDLINE                          DUPLICATE 6
ACCESSION NUMBER:    2001335647     MEDLINE
DOCUMENT NUMBER:     21296319   PubMed ID: 11402584
TITLE:               Oral drug therapy for erectile dysfunction.
AUTHOR:              Padma-Nathan H; Giuliano F
CORPORATE SOURCE:    Department of Urology, Keck School of Medicine, University
                     of Southern California Beverly Hills, California, USA.
SOURCE:              UROLOGIC CLINICS OF NORTH AMERICA, (2001 May) 28 (2)
                     321-34.  Ref: 39
                     Journal code: 0423221. ISSN: 0094-0143.
PUB. COUNTRY:        United States
                     Journal; Article; (JOURNAL ARTICLE)
```

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

AB Oral drugs are a well-established, first-line therapy for erectile dysfunction. As a result of the success of sildenafil, a plethora of new drugs for erectile dysfunction are on the horizon. Apomorphine and **IC351** are in late phase III development. Vardenafil (Bayer, New Haven, CT), a PDE5 inhibitor, and the combination of yohimbine and L-arginine (NitroMed, Boston, MA) are in early phase III development. Early clinical and preclinical studies are investigating new phosphodiesterase inhibitors, cyclic AMP activators, alpha-adrenergic antagonists, dopamine agonists, melanocyte-stimulating hormone, potassium channel modulators, endothelin antagonists, and new nitric oxide donors. The future is bright for this infant field of sexual pharmacotherapy.

L25 ANSWER 39 OF 58 MEDLINE
ACCESSION NUMBER: 2002117405 MEDLINE
DOCUMENT NUMBER: 21838816 PubMed ID: 11850737
TITLE: **IC351** (tadalafil, Cialis): update on clinical experience.
AUTHOR: Porst H
CORPORATE SOURCE: Urological practice, Hamburg, Germany.. Porst20354@aol.com
SOURCE: INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, (2002 Feb) 14 Suppl 1 S57-64. Ref: 12
Journal code: 9007383. ISSN: 0955-9930.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020220
Last Updated on STN: 20020613
Entered Medline: 20020612

AB **IC351** (tadalafil, trade name Cialis) is a new representative compound of the second generation of selective phosphodiesterase 5 (PDE-5) inhibitors. The selectivity ratio vs PDE-5 is more than 10 000 for PDE-1 through PDE-4 and PDE-7 through PDE-10 and 780 for PDE-6. In the European daily-dosing trial, the efficacy rates were up to 93% for successful intercourses with completion in the 50-mg dose in patients with mild to moderate erectile dysfunction (ED). In two different dose-ranging studies with 2-25 mg taken as needed, efficacy rates of up to 88% improvement in erections and up to 73% successful intercourses with completion were achieved. In a placebo-controlled, fixed-dose (10- and 20-mg) trial in diabetic patients, improved erections of 56% and 64% were reported compared with 25% after placebo. Drug-related adverse effects, with headache in up to 23% of patients (placebo, up to 17%), dyspepsia in up to 11% (placebo, up to 7%), back pain in up to 4.7% (placebo, 0%), and myalgia in up to 4.1% (placebo, up to 2.4%), were mostly mild to moderate. Neither drug-related serious cardiovascular adverse events nor color vision disturbances were encountered. The long half-life (>17 h), with a comfortably long window of opportunity, releases couples from the need to plan sexual activities and therefore provides the highest amount of spontaneity for sexual activities.

L25 ANSWER 40 OF 58 MEDLINE
ACCESSION NUMBER: 2002073964 MEDLINE
DOCUMENT NUMBER: 21658223 PubMed ID: 11799971
TITLE: Towards optimal ED management: educational forum - II.
AUTHOR: Brock G
CORPORATE SOURCE: Division of Urology, Department of Surgery, University of Western Ontario, London, Ontario.
SOURCE: Can J Urol, (2001 Dec) 8 (6) 1419-20.
Journal code: 9515842. ISSN: 1195-9479.
PUB. COUNTRY: Canada
Conference; Conference Article; (CONGRESSES)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020206
Entered Medline: 20020205

L25 ANSWER 41 OF 58 MEDLINE
ACCESSION NUMBER: 2001342867 MEDLINE
DOCUMENT NUMBER: 21298873 PubMed ID: 11406522
TITLE: Importance of NF-kappaB in rheumatoid synovial tissues: in situ NF-kappaB expression and in vitro study using cultured synovial cells.
AUTHOR: Yamasaki S; Kawakami A; Nakashima T; Nakamura H; Kamachi M; Honda S; Hirai Y; Hida A; Ida H; Migita K; Kawabe Y; Koji T; Furuichi I; Aoyagi T; Eguchi K
CORPORATE SOURCE: The First Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki, Japan.
SOURCE: ANNALS OF THE RHEUMATIC DISEASES, (2001 Jul) 60 (7) 678-84.
Journal code: 0372355. ISSN: 0003-4967.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010716
Last Updated on STN: 20010716
Entered Medline: 20010712

AB OBJECTIVES: To examine whether inhibition of NF-kappaB induces apoptosis of human synovial cells stimulated by tumour necrosis factor alpha (TNFalpha), interleukin 1beta (IL1beta), and anti-Fas monoclonal antibody (mAb). METHODS: The expression of proliferating cell nuclear antigen (PCNA), NF-kappaB, and the presence of apoptotic synovial cells were determined in synovial tissues. Apoptosis of cultured synovial cells was induced by inhibition of NF-kappaB nuclear translocation by Z-Leu-Leu-Leu-aldehyde (LLL-CHO). The activation of caspase-3 and expression of XIAP and cIAP2 in synovial cells in LLL-CHO induced apoptosis was also examined. RESULTS: Abundant PCNA+ synovial cells were found in rheumatoid arthritis (RA) synovial tissue, though a few apoptotic synovial cells were also detected in the RA synovial tissues. Nuclear NF-kappaB was expressed in RA synovial cells. Electrophoretic mobility shift assay showed that treatment of cells with TNFalpha or IL1beta significantly stimulated nuclear NF-kappaB activity. A small number of apoptotic synovial cells expressing intracellular active caspase-3 were found after treatment of cells with LLL-CHO. Although treatment of RA synovial cells with TNFalpha or IL1beta alone did not induce apoptosis, apoptosis induced by LLL-CHO and caspase-3 activation were clearly enhanced in TNFalpha or IL1beta stimulated synovial cells compared with unstimulated synovial cells. Furthermore, induction of apoptosis of

synovial cells with caspase-3 activation by anti-Fas mAb was clearly increased by LLL-CHO. The expression of cIAP2 and XIAP in synovial cells may not directly influence the sensitivity of synovial cells to apoptosis induced by LLL-CHO. CONCLUSION: The results suggest that NF-kappaB inhibition may be a potentially important therapeutic approach for RA by correcting the imbalance between apoptosis and proliferation of synovial cells in RA synovial tissue.

L25 ANSWER 42 OF 58 MEDLINE
ACCESSION NUMBER: 2001382350 MEDLINE
DOCUMENT NUMBER: 21213761 PubMed ID: 11313831
TITLE: On-demand **IC351** (Cialis) enhances erectile function in patients with erectile dysfunction.
AUTHOR: Padma-Nathan H; McMurray J G; Pullman W E; Whitaker J S; Saoud J B; Ferguson K M; Rosen R C
CORPORATE SOURCE: Keck School of Medicine, University of Southern California, Los Angeles, California 90212, USA. (IC351 On-Demand Dosing Study Group).
SOURCE: INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, (2001 Feb) 13 (1) 2-9.
Journal code: 9007383. ISSN: 0955-9930.
PUB. COUNTRY: England: United Kingdom
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB **IC351** (Cialis) is a selective inhibitor of PDE5. The efficacy and safety of on-demand dosing of **IC351** in men with erectile dysfunction was assessed in a multicenter, double-blind, placebo-controlled study. One hundred seventy-nine men (mean age: 56 y) were randomized to receive placebo or **IC351** at doses of 2, 5, 10 or 25 mg, taken on demand over a 3-week period. The primary endpoints were change from baseline in responses to Questions 3 (Q3) and 4 (Q4) of the International Index of Erectile Function (IIEF). **IC351** significantly improved IIEF Q3 scores at all doses vs placebo ($P < or = 0.003$). **IC351** also significantly improved IIEF Q4 scores in all but the 2 mg group ($P < or = 0.0003$). No significant changes in laboratory values, ECGs, or blood pressure were observed. The most common adverse events were headache and dyspepsia. The conclusion of this study was that on-demand **IC351** at doses up to 25 mg was well tolerated and significantly improved erectile function.

L25 ANSWER 43 OF 58 MEDLINE
ACCESSION NUMBER: 2002005986 MEDLINE
DOCUMENT NUMBER: 21064306 PubMed ID: 11122955
TITLE: Recent developments in male sexual dysfunction.
AUTHOR: Shabsigh R
CORPORATE SOURCE: Department of Urology, Columbia-Presbyterian Medical Center, 161 Fort Washington Avenue, New York, NY 10032, USA.. rs66@columbia.edu
SOURCE: Curr Psychiatry Rep, (2000 Jun) 2 (3) 196-200. Ref: 8
Journal code: 100888960. ISSN: 1523-3812.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020501
Entered Medline: 20020430

AB The past few years have witnessed major developments in the management of male sexual dysfunction. The introduction of the first efficacious and safe oral medication (sildenafil) resulted in the expansion of the patient base and, the change in health care delivery, with erectile dysfunction (ED) entering the primary care physician's practice. New guidelines for the diagnosis and treatment of ED have been developed, including the Process of Care in the USA and the 1st International Consultation on ED sponsored by the World Health Organization. Well-defined algorithms for diagnosis and treatment have been adopted. These recent developments have brought up challenging issues, including the cardiovascular safety of sexual activity, societal changes, internet prescriptions, definition of the patient, expansion of clinical and laboratory research, rise of interest in female sexual dysfunction, and a significant economic impact. The recent developments in male sexual dysfunction continue with the study of new oral medications. Some of these new medications, such as sublingual apomorphine, have a central mode of action, whereas others, such as the phosphodiesterase inhibitor **IC351**, have a selective peripheral vasodilation-enhancing action.

L25 ANSWER 44 OF 58 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-572170 [53] WPIDS
DOC. NO. CPI: C2000-170623
TITLE: New nitrosated and nitrosylated prostaglandins, useful for treating or preventing e.g. sexual dysfunction in males and females, cerebrovascular disorders and glaucoma.
DERWENT CLASS: B05
INVENTOR(S): GARVEY, D S; GASTON, R D; LETTS, G L; SAENZ DE TEJADA, I; TAM, S W; WORCEL, M
PATENT ASSIGNEE(S): (NITR-N) NITROMED INC
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000051978	A1	20000908	(200053)*	EN	82
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM 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					
AU 2000037136	A	20000921	(200065)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000051978	A1	WO 2000-US5286	20000301
AU 2000037136	A	AU 2000-37136	20000301

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2000037136 A Based on WO 200051978

PRIORITY APPLN. INFO: US 1999-138502P 19990609; US 1999-122273P 19990301

AB WO 200051978 A UPAB: 20001023

NOVELTY - Nitrosated and nitrosylated prostaglandins (I) and compositions comprising them are new, also compositions comprising a prostaglandin and S-nitrosothiol compound.

DETAILED DESCRIPTION - Nitrosated and nitrosylated prostaglandins of formula (I) are new:

bonds a', b', c', d' = single or double bonds;

R1 = -OD1 or Cl;

R2, R8 = H; or

R1+R2 = =CH2 or =O;

R3, R4 = H, -OD1 or Me;

R5, R6 = H, -OD1, Me, OMe or -CH=CH2;

R7 = H or OD1;

R9 = H or absent when the C to which it is attached is the central carbon of an allene; or

R8+R9+attached chain atoms = a substituted benzene ring provided that R1 is O which is attached to the C at the position of the benzene ring defined by B';

A = -CH=, -CH2-, -S- or -O-;

B' = -CH=, -CH2-, -S- or -C(O)-;

X = -CH2OR11, -C(O)OR11 or -C(O)N(D1)R12;

R11 = D1, 1-10C alkyl or a group of formula (i):

R12 = -S(O)2CH3 or -C(O)CH3;

Z' = ethyl, butyl, hexyl, benzyl, -CH2-O-CH2-CH3, -CH(CH3)-(CH2)3-CH3 or a group of formula (ii) or (iii):

R13 = H or Cl;

D1 = H or D; provided that at least 1 D1 is D;

D = Q or K;

Q = -NO or NO2;

K = -Wa-Eb-(C(Re)(Rf))p-Ec-(C(Re)(Rf))x-Wd -(C(Re)(Rf))y-Wi-Ej-Wg-(C(Re)(Rf))z-T-Q;

a, b, c, d, g, i, j = 0-3;

p, x, y, z = 0-10;

E = -T-, alkyl, aryl, (C(Re)(Rf))h-,

W = -C(O)-, -C(S)- or as defined for E;

h = 1 10;

q = 1-5;

Re, Rf = H, alkyl, cycloalkoxy, halo, OH, hydroxyalkyl, alkoxyalkyl, aryl-heterocyclic, alkylaryl, cycloalkylalkyl, heterocyclic-alkyl, alkoxy, haloalkoxy, NH2, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkoxyhaloalkyl, haloalkoxy, sulfonic acid, sulfonic ester, alkylsulfonic acid, arylsulfonic acid, arylalkoxy, alkylthio, arylthio, cycloalkylthio, cycloalkenyl, CN, aminoalkyl, aminoaryl, aryl, arylalkyl, alkylaryl, carboxamido, alkylcarboxamido, arylcarboxamido, amidyl, carboxyl, carbamoyl, alkylcarboxylic acid, arylcarboxylic acid, alkylcarbonyl, arylcarbonyl, ester, carboxylic ester, alkylcarboxylic ester, arylcarboxylic ester, haloalkoxy, sulfonamido, alkylsulfonamido, arylsulfonamido, sulfonic ester, a urea, phosphoryl, nitro, -T-Q or -(C(Re)(Rf))k-T-Q; or

Re+Rf+attached C atoms = carbonyl, methanthial, heterocyclic, cycloalkyl or a bridged cycloalkyl;

k = 1-3;

T = a covalent bond, carbonyl, O, -S(O)o- or -N(Ra)Ri-;

o = 0-2;

Ra = a lone pair of electrons, H or alkyl;

Ri = H, alkyl, aryl, alkylcarboxylic acid, arylcarboxylic acid,

alkylcarboxylic ester, arylcarboxylic ester, alkylcarboxamido, arylcarboxamido, alkylaryl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, sulfonamido, carboxamido, carboxylic ester, amino alkyl, amino aryl, -CH2-C(T-Q)(Re)(Rf) or -(N2O2)-M+;

M+ = an organic or inorganic cation;

provided that when Ri is -CH2-C(T-Q)(Re)(Rf) or -(N2O2) M+; or Re or Rf are T-Q or (C(Re)(Rf))k-T-Q, then T-Q can be H, alkyl, alkoxy, alkoxyalkyl, aminoalkyl, OH, heterocyclic or aryl; and provided that when X is -C(O)OD1 and D1 is K, then K is not alkyl or cycloalkyl mononitrate; benzoic acid substituted benzyloxy mononitrate; ethylene glycol mononitrate; polyethylene glycol mononitrate; the regioisomeric esters of glycerol dinitrate and oligomers as disclosed in WO9858910.

INDEPENDENT CLAIMS are included for the following:

(a) compositions and kits comprising (I) and at least 1 compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, and/or at least 1 vasoactive agent; and

(b) compositions and kits comprising at least 1 prostaglandin and at least 1 S-nitrosothiol compound, useful for treating sexual dysfunction, a cerebrovascular disorder, cardiovascular disorder, benign prostatic hyperplasia, organ transplants, glaucoma or peptic ulcer, or for inducing an abortion.

ACTIVITY - Vasotropic; Cerebroprotective; Cardiant; Cytostatic; Ophthalmological; Antiulcer; Gynecological; Relaxant.

MECHANISM OF ACTION - Smooth muscle relaxant; Nitric oxide donor; Endothelium-derived relaxing factor agonist.

USE - For treating or preventing sexual dysfunction in males or females, treating a cerebrovascular disorder, cardiovascular disorder, benign prostatic hyperplasia, organ transplants, glaucoma or peptic ulcer, or for inducing an abortion (all claimed).

ADVANTAGE - The combination of a prostaglandin and a S-nitrosothiol gives synergistic results.

Dwg.0/4

L25 ANSWER 45 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:355438 BIOSIS
DOCUMENT NUMBER: PREV200200355438
TITLE: Efficacy and safety of **tadalafil** in men with erectile dysfunction with and without hypertension.
AUTHOR(S): Padma-Nathan, H. (1); Brock, G.; McMahon, C.; Chen, K. K.; Anglin, G.; Costigan, T.; Shen, W.; Watkins, V.; Whitaker, J. S.
CORPORATE SOURCE: (1) Keck School of Medicine, University of Southern California, Beverly Hills, CA USA
SOURCE: American Journal of Hypertension, (April, 2002) Vol. 15, No. 4 Part 2, pp. 143A-144A. http://www.ajh-us.org. print. Meeting Info.: Seventeenth Annual Scientific Meeting of the American Society of Hypertension New York, N.Y., USA May 14-18, 2002
ISSN: 0895-7061.
DOCUMENT TYPE: Conference
LANGUAGE: English

L25 ANSWER 46 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:355428 BIOSIS
DOCUMENT NUMBER: PREV200200355428
TITLE: Blood pressure and cardiovascular effects of **tadalafil**, a new PDE5 inhibitor.
AUTHOR(S): Hutter, A. M. (1); Kloner, R. A.; Watkins, V.; Costigan, T.; Bedding, A.; Mitchell, M.; Emmick, J.

CORPORATE SOURCE: (1) Massachusetts General Hospital, Harvard Medical School, Boston, MA USA
SOURCE: American Journal of Hypertension, (April, 2002) Vol. 15, No. 4 Part 2, pp. 140A. http://www.ajh-us.org. print.
Meeting Info.: Seventeenth Annual Scientific Meeting of the American Society of Hypertension New York, N.Y., USA May 14-18, 2002
ISSN: 0895-7061.
DOCUMENT TYPE: Conference
LANGUAGE: English

L25 ANSWER 47 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:449004 BIOSIS
DOCUMENT NUMBER: PREV200100449004
TITLE: CialisTM (**IC351**) as a treatment of erectile dysfunction in diabetic men.
AUTHOR(S): Saenz De Tejada, Inigo (1); Fredlund, Paul (1); Anglin, Greg (1); Pullman, Bill (1); Emmick, Jeff (1)
CORPORATE SOURCE: (1) Madrid Spain
SOURCE: Diabetes, (June, 2001) Vol. 50, No. Supplement 2, pp. A425. print.
Meeting Info.: 61st Scientific Sessions of the American Diabetes Association Philadelphia, Pennsylvania, USA June 22-26, 2001
ISSN: 0012-1797.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 48 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:380171 BIOSIS
DOCUMENT NUMBER: PREV200100380171
TITLE: CialisTM (**IC351**) provides prompt response and extended period of responsiveness for the treatment of men with erectile dysfunction (ED.
AUTHOR(S): Padma-Nathan, Harin (1); Rosen, Raymond C.; Shabsigh, Ridwan; Saikali, Khalil; Watkins, Vish S.; Pullman, Bill
CORPORATE SOURCE: (1) Los Angeles, CA USA
SOURCE: Journal of Urology, (May, 2001) Vol. 165, No. 5 Supplement, pp. 224. print.
Meeting Info.: Annual Meeting of the American Urological Association, Inc. Anaheim, California, USA June 02-07, 2001
ISSN: 0022-5347.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 49 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:381536 BIOSIS
DOCUMENT NUMBER: PREV200100381536
TITLE: Cellular localisation of phosphodiesterase type 11 (PDE11) in human corpus cavernosum and the contribution of PDE11 inhibition on nerve-stimulated relaxation.
AUTHOR(S): Baxendale, Rhona W. (1); Wayman, Christopher P. (1); Turner, Leigh (1); Phillips, Stephen C. (1)
CORPORATE SOURCE: (1) Sandwich UK
SOURCE: Journal of Urology, (May, 2001) Vol. 165, No. 5 Supplement, pp. 223-224. print.
Meeting Info.: Annual Meeting of the American Urological Association, Inc. Anaheim, California, USA June 02-07, 2001
ISSN: 0022-5347.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 50 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:262700 BIOSIS
DOCUMENT NUMBER: PREV200100262700
TITLE: CialisTM (**IC351**): Effective and well-tolerated treatment for ED.
AUTHOR(S): Brock, G. (1); Iglesias, J.; Toulouse, K.; Ferguson, K.; Pullman, W.; Anglin, G.
CORPORATE SOURCE: (1) Univ W Ontario, London, ON Canada
SOURCE: Journal of Andrology, (May June, 2001) No. Supplement, pp. 185. print.
Meeting Info.: VIIth International Congress of Andrology Montreal, Canada June 15-19, 2001
ISSN: 0196-3635.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 51 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:389604 BIOSIS
DOCUMENT NUMBER: PREV200100389604
TITLE: Efficacy and safety of **IC351** treatment for ED.
AUTHOR(S): Brock, G. (1); Iglesias, J.; Toulouse, K.; Ferguson, K.; Pullman, W.; Anglin, G.
CORPORATE SOURCE: (1) Univ. of W. Ontario, London, ON Canada
SOURCE: European Urology, (March, 2001) Vol. 39, No. Suppl. 5, pp. 106. print.
Meeting Info.: XVIth Congress of the European Association of Urology Geneva, Switzerland April 07-10, 2001
ISSN: 0302-2838.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 52 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:391998 BIOSIS
DOCUMENT NUMBER: PREV200100391998
TITLE: **IC351** enhances NO-mediated relaxation of human arterial and trabecular penile smooth muscle.
AUTHOR(S): Angulo, J. (1); Gadau, M.; Fernandez, A.; Gabancho, S.; Cuevas, P.; Martins, T.; Florio, V.; Ferguson, K.; Saenz De Tejada, I.
CORPORATE SOURCE: (1) Hospital Ramon y Cajal, Madrid Spain
SOURCE: European Urology, (March, 2001) Vol. 39, No. Suppl. 5, pp. 106. print.
Meeting Info.: XVIth Congress of the European Association of Urology Geneva, Switzerland April 07-10, 2001
ISSN: 0302-2838.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 53 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:375151 BIOSIS
DOCUMENT NUMBER: PREV200100375151
TITLE: The effect of on-demand **IC351** treatment of erectile dysfunction in men with diabetes.
AUTHOR(S): Saenz De Tejada, Inigo (1); Emmick, J.; Anglin, G.;

Fredlund, P.; Pullman, W.
CORPORATE SOURCE: (1) Hospital Ramon y Cajal, Madrid Spain
SOURCE: European Urology, (March, 2001) Vol. 39, No. Suppl. 5, pp. 16. print.
Meeting Info.: XVIth Congress of the European Association of Urology Geneva, Switzerland April 07-10, 2001
ISSN: 0302-2838.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 54 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:211709 BIOSIS
DOCUMENT NUMBER: PREV200000211709
TITLE: Daily and on-demand **IC351** treatment of erectile dysfunction.
AUTHOR(S): Giuliano, Francois (1); Porst, Hartmut; Padma-Nathan, Harin; Saoud, Jay; Ferguson, Kenneth; Whitaker, Steven; Pullman, William; Rosen, Raymond
CORPORATE SOURCE: (1) Bicetre France
SOURCE: Journal of Urology, (April, 2000) Vol. 163, No. 4 Suppl., pp. 201.
Meeting Info.: 95th Annual Meeting of the American Urological Association, Inc. Atlanta, Georgia, USA April 29, 2000-May 04, 1999
ISSN: 0022-5347.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 55 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:356087 BIOSIS
DOCUMENT NUMBER: PREV200000356087
TITLE: On-demand treatment of erectile dysfunction with **IC351**.
AUTHOR(S): Padma-Nathan, Harin (1); McMurray, James; Saoud, Jay; Ferguson, Kenneth; Pullman, William; Whitaker, Steven; Rosen, Raymond
CORPORATE SOURCE: (1) Male Clinic, University of Southern California, Santa Monica, CA USA
SOURCE: European Urology, (March, 2000) Vol. 37, No. Suppl. 2, pp. 80. print.
Meeting Info.: XVth Congress of the European Association of Urology Brussels, Belgium April 12-15, 2000
ISSN: 0302-2838.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 56 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:356088 BIOSIS
DOCUMENT NUMBER: PREV200000356088
TITLE: Daily **IC351** treatment of erectile dysfunction.
AUTHOR(S): Giuliano, Francois (1); Meuleman, Eric; Saoud, Jay; Ferguson, Kenneth; Whitaker, Steven; Porst, Hartmut
CORPORATE SOURCE: (1) Department of Urology, University Hospital of Bicetre, Le Kremlin France
SOURCE: European Urology, (March, 2000) Vol. 37, No. Suppl. 2, pp. 80. print.
Meeting Info.: XVth Congress of the European Association of Urology Brussels, Belgium April 12-15, 2000

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L21          16 SEA FILE=BIOSIS ABB=ON  PLU=ON  CIALIS OR IC351 OR (IC OR
                ICOS) (W) (351) OR TADALAFIL OR TARDANAFIL OR GF196960 OR GF
                (W) (196960 OR 196 960)


=> file medline; d que 123
FILE 'MEDLINE' ENTERED AT 15:02:56 ON 16 JUL 2002

 FILE LAST UPDATED: 13 JUL 2002 (20020713/UP).  FILE COVERS 1958 TO DATE.

 On June 9, 2002, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2002 vocabulary.  Enter HELP THESAURUS for details.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.

L23           6 SEA FILE=MEDLINE ABB=ON  PLU=ON  IC351


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FILE 'MEDLINE' ENTERED AT 15:03:25 ON 16 JUL 2002

FILE 'WPIDS' ENTERED AT 15:03:25 ON 16 JUL 2002
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PROCESSING COMPLETED FOR L19
PROCESSING COMPLETED FOR L21
L24          30 DUP REM L23 L19 L21 L23 (1 DUPLICATE REMOVED)
                ANSWERS '1-6' FROM FILE MEDLINE
                ANSWERS '7-15' FROM FILE WPIDS
                ANSWERS '16-30' FROM FILE BIOSIS

=> dup rem l12 l23 l19 l21 l23
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FILE 'WPIDS' ENTERED AT 15:04:37 ON 16 JUL 2002
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FILE 'BIOSIS' ENTERED AT 15:04:37 ON 16 JUL 2002
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PROCESSING COMPLETED FOR L12
PROCESSING COMPLETED FOR L23
PROCESSING COMPLETED FOR L19
PROCESSING COMPLETED FOR L21
L25          58 DUP REM L12 L23 L19 L21 L23 (10 DUPLICATES REMOVED)
                ANSWERS '1-37' FROM FILE CAPLUS
                ANSWERS '38-43' FROM FILE MEDLINE
                ANSWER '44' FROM FILE WPIDS
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ANSWERS '45-58' FROM FILE BIOSIS

=> d ibib ab l25 38-58

L25 ANSWER 38 OF 58 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2001335647 MEDLINE
DOCUMENT NUMBER: 21296319 PubMed ID: 11402584
TITLE: Oral drug therapy for erectile dysfunction.
AUTHOR: Padma-Nathan H; Giuliano F
CORPORATE SOURCE: Department of Urology, Keck School of Medicine, University of Southern California Beverly Hills, California, USA.
SOURCE: UROLOGIC CLINICS OF NORTH AMERICA, (2001 May) 28 (2) 321-34. Ref: 39
Journal code: 0423221. ISSN: 0094-0143.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628
AB Oral drugs are a well-established, first-line therapy for erectile dysfunction. As a result of the success of sildenafil, a plethora of new drugs for erectile dysfunction are on the horizon. Apomorphine and **IC351** are in late phase III development. Vardenafil (Bayer, New Haven, CT), a PDE5 inhibitor, and the combination of yohimbine and L-arginine (NitroMed, Boston, MA) are in early phase III development. Early clinical and preclinical studies are investigating new phosphodiesterase inhibitors, cyclic AMP activators, alpha-adrenergic antagonists, dopamine agonists, melanocyte-stimulating hormone, potassium channel modulators, endothelin antagonists, and new nitric oxide donors. The future is bright for this infant field of sexual pharmacotherapy.

L25 ANSWER 39 OF 58 MEDLINE
ACCESSION NUMBER: 2002117405 MEDLINE
DOCUMENT NUMBER: 21838816 PubMed ID: 11850737
TITLE: **IC351** (tadalafil, Cialis): update on clinical experience.
AUTHOR: Porst H
CORPORATE SOURCE: Urological practice, Hamburg, Germany.. Porst20354@aol.com
SOURCE: INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, (2002 Feb) 14 Suppl 1 S57-64. Ref: 12
Journal code: 9007383. ISSN: 0955-9930.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020220
Last Updated on STN: 20020613
Entered Medline: 20020612
AB **IC351** (tadalafil, trade name Cialis) is a new representative compound of the second generation of selective phosphodiesterase 5 (PDE-5) inhibitors. The selectivity ratio vs PDE-5 is more than 10 000 for PDE-1 through PDE-4 and PDE-7 through PDE-10 and 780 for PDE-6. In the European daily-dosing trial, the efficacy rates were up to 93% for successful

intercourses with completion in the 50-mg dose in patients with mild to moderate erectile dysfunction (ED). In two different dose-ranging studies with 2-25 mg taken as needed, efficacy rates of up to 88% improvement in erections and up to 73% successful intercourses with completion were achieved. In a placebo-controlled, fixed-dose (10- and 20-mg) trial in diabetic patients, improved erections of 56% and 64% were reported compared with 25% after placebo. Drug-related adverse effects, with headache in up to 23% of patients (placebo, up to 17%), dyspepsia in up to 11% (placebo, up to 7%), back pain in up to 4.7% (placebo, 0%), and myalgia in up to 4.1% (placebo, up to 2.4%), were mostly mild to moderate. Neither drug-related serious cardiovascular adverse events nor color vision disturbances were encountered. The long half-life (>17 h), with a comfortably long window of opportunity, releases couples from the need to plan sexual activities and therefore provides the highest amount of spontaneity for sexual activities.

L25 ANSWER 40 OF 58 MEDLINE
ACCESSION NUMBER: 2002073964 MEDLINE
DOCUMENT NUMBER: 21658223 PubMed ID: 11799971
TITLE: Towards optimal ED management: educational forum - II.
AUTHOR: Brock G
CORPORATE SOURCE: Division of Urology, Department of Surgery, University of Western Ontario, London, Ontario.
SOURCE: Can J Urol, (2001 Dec) 8 (6) 1419-20.
Journal code: 9515842. ISSN: 1195-9479.
PUB. COUNTRY: Canada
Conference; Conference Article; (CONGRESSES)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020206
Entered Medline: 20020205

L25 ANSWER 41 OF 58 MEDLINE
ACCESSION NUMBER: 2001342867 MEDLINE
DOCUMENT NUMBER: 21298873 PubMed ID: 11406522
TITLE: Importance of NF-kappaB in rheumatoid synovial tissues: in situ NF-kappaB expression and in vitro study using cultured synovial cells.
AUTHOR: Yamasaki S; Kawakami A; Nakashima T; Nakamura H; Kamachi M; Honda S; Hirai Y; Hida A; Ida H; Migita K; Kawabe Y; Koji T; Furuichi I; Aoyagi T; Eguchi K
CORPORATE SOURCE: The First Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki, Japan.
SOURCE: ANNALS OF THE RHEUMATIC DISEASES, (2001 Jul) 60 (7) 678-84.
Journal code: 0372355. ISSN: 0003-4967.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010716
Last Updated on STN: 20010716
Entered Medline: 20010712
AB OBJECTIVES: To examine whether inhibition of NF-kappaB induces apoptosis of human synovial cells stimulated by tumour necrosis factor alpha (TNFalpha), interleukin 1beta (IL1beta), and anti-Fas monoclonal antibody (mAb). METHODS: The expression of proliferating cell nuclear antigen (PCNA), NF-kappaB, and the presence of apoptotic synovial cells were

determined in synovial tissues. Apoptosis of cultured synovial cells was induced by inhibition of NF-kappaB nuclear translocation by Z-Leu-Leu-Leu-aldehyde (LLL-CHO). The activation of caspase-3 and expression of XIAP and cIAP2 in synovial cells in LLL-CHO induced apoptosis was also examined. RESULTS: Abundant PCNA+ synovial cells were found in rheumatoid arthritis (RA) synovial tissue, though a few apoptotic synovial cells were also detected in the RA synovial tissues. Nuclear NF-kappaB was expressed in RA synovial cells. Electrophoretic mobility shift assay showed that treatment of cells with TNFalpha or IL1beta significantly stimulated nuclear NF-kappaB activity. A small number of apoptotic synovial cells expressing intracellular active caspase-3 were found after treatment of cells with LLL-CHO. Although treatment of RA synovial cells with TNFalpha or IL1beta alone did not induce apoptosis, apoptosis induced by LLL-CHO and caspase-3 activation were clearly enhanced in TNFalpha or IL1beta stimulated synovial cells compared with unstimulated synovial cells. Furthermore, induction of apoptosis of synovial cells with caspase-3 activation by anti-Fas mAb was clearly increased by LLL-CHO. The expression of cIAP2 and XIAP in synovial cells may not directly influence the sensitivity of synovial cells to apoptosis induced by LLL-CHO. CONCLUSION: The results suggest that NF-kappaB inhibition may be a potentially important therapeutic approach for RA by correcting the imbalance between apoptosis and proliferation of synovial cells in RA synovial tissue.

L25 ANSWER 42 OF 58 MEDLINE
ACCESSION NUMBER: 2001382350 MEDLINE
DOCUMENT NUMBER: 21213761 PubMed ID: 11313831
TITLE: On-demand **IC351** (Cialis) enhances erectile function in patients with erectile dysfunction.
AUTHOR: Padma-Nathan H; McMurray J G; Pullman W E; Whitaker J S; Saoud J B; Ferguson K M; Rosen R C
CORPORATE SOURCE: Keck School of Medicine, University of Southern California, Los Angeles, California 90212, USA. (IC351 On-Demand Dosing Study Group).
SOURCE: INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, (2001 Feb) 13 (1) 2-9.
Journal code: 9007383. ISSN: 0955-9930.
PUB. COUNTRY: England: United Kingdom
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB **IC351** (Cialis) is a selective inhibitor of PDE5. The efficacy and safety of on-demand dosing of **IC351** in men with erectile dysfunction was assessed in a multicenter, double-blind, placebo-controlled study. One hundred seventy-nine men (mean age: 56 y) were randomized to receive placebo or **IC351** at doses of 2, 5, 10 or 25 mg, taken on demand over a 3-week period. The primary endpoints were change from baseline in responses to Questions 3 (Q3) and 4 (Q4) of the International Index of Erectile Function (IIEF). **IC351** significantly improved IIEF Q3 scores at all doses vs placebo (P < or =0.003). **IC351** also significantly improved IIEF Q4 scores in all but the 2 mg group (P < or =0.0003). No significant changes in laboratory values, ECGs, or blood pressure were observed. The most common adverse events were headache and dyspepsia. The conclusion of this study was that

on-demand **IC351** at doses up to 25 mg was well tolerated and significantly improved erectile function.

L25 ANSWER 43 OF 58 MEDLINE
ACCESSION NUMBER: 2002005986 MEDLINE
DOCUMENT NUMBER: 21064306 PubMed ID: 11122955
TITLE: Recent developments in male sexual dysfunction.
AUTHOR: Shabsigh R
CORPORATE SOURCE: Department of Urology, Columbia-Presbyterian Medical Center, 161 Fort Washington Avenue, New York, NY 10032, USA.. rs66@columbia.edu
SOURCE: Curr Psychiatry Rep, (2000 Jun) 2 (3) 196-200. Ref: 8
Journal code: 100888960. ISSN: 1523-3812.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020501
Entered Medline: 20020430

AB The past few years have witnessed major developments in the management of male sexual dysfunction. The introduction of the first efficacious and safe oral medication (sildenafil) resulted in the expansion of the patient base and, the change in health care delivery, with erectile dysfunction (ED) entering the primary care physician's practice. New guidelines for the diagnosis and treatment of ED have been developed, including the Process of Care in the USA and the 1st International Consultation on ED sponsored by the World Health Organization. Well-defined algorithms for diagnosis and treatment have been adopted. These recent developments have brought up challenging issues, including the cardiovascular safety of sexual activity, societal changes, internet prescriptions, definition of the patient, expansion of clinical and laboratory research, rise of interest in female sexual dysfunction, and a significant economic impact. The recent developments in male sexual dysfunction continue with the study of new oral medications. Some of these new medications, such as sublingual apomorphine, have a central mode of action, whereas others, such as the phosphodiesterase inhibitor **IC351**, have a selective peripheral vasodilation-enhancing action.

L25 ANSWER 44 OF 58 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-572170 [53] WPIDS
DOC. NO. CPI: C2000-170623
TITLE: New nitrosated and nitrosylated prostaglandins, useful for treating or preventing e.g. sexual dysfunction in males and females, cerebrovascular disorders and glaucoma.
DERWENT CLASS: B05
INVENTOR(S): GARVEY, D S; GASTON, R D; LETTS, G L; SAENZ DE TEJADA, I; TAM, S W; WORCEL, M
PATENT ASSIGNEE(S): (NITR-N) NITROMED INC
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000051978	A1	20000908	(200053)*	EN	82

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM 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
AU 2000037136 A 20000921 (200065)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000051978 A1		WO 2000-US5286	20000301
AU 2000037136 A		AU 2000-37136	20000301

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000037136 A	Based on	WO 200051978

PRIORITY APPLN. INFO: US 1999-138502P 19990609; US 1999-122273P 19990301

AB WO 200051978 A UPAB: 20001023
NOVELTY - Nitrosated and nitrosylated prostaglandins (I) and compositions comprising them are new, also compositions comprising a prostaglandin and S-nitrosothiol compound.
DETAILED DESCRIPTION - Nitrosated and nitrosylated prostaglandins of formula (I) are new:
bonds a', b', c', d' = single or double bonds;
R1 = -OD1 or Cl;
R2, R8 = H; or
R1+R2 = =CH2 or =O;
R3, R4 = H, -OD1 or Me;
R5, R6 = H, -OD1, Me, OMe or -CH=CH2;
R7 = H or OD1;
R9 = H or absent when the C to which it is attached is the central carbon of an allene; or
R8+R9+attached chain atoms = a substituted benzene ring provided that R1 is O which is attached to the C at the position of the benzene ring defined by B';
A = -CH=, -CH2-, -S- or -O-;
B' = -CH=, -CH2-, -S- or -C(O)-;
X = -CH2OR11, -C(O)OR11 or -C(O)N(D1)R12;
R11 = D1, 1-10C alkyl or a group of formula (i):
R12 = -S(O)2CH3 or -C(O)CH3;
Z' = ethyl, butyl, hexyl, benzyl, -CH2-O-CH2-CH3, -CH(CH3)-(CH2)3-CH3 or a group of formula (ii) or (iii):
R13 = H or Cl;
D1 = H or D; provided that at least 1 D1 is D;
D = Q or K;
Q = -NO or NO2;
K = -Wa-Eb-(C(Re)(Rf))p-Ec-(C(Re)(Rf))x-Wd -(C(Re)(Rf))y-Wi-Ej-Wg-(C(Re)(Rf))z-T-Q;
a, b, c, d, g, i, j = 0-3;
p, x, y, z = 0-10;
E = -T-, alkyl, aryl, (C(Re)(Rf))h-,
W = -C(O)-, -C(S)- or as defined for E;
h = 1 10;
q = 1-5;
Re, Rf = H, alkyl, cycloalkoxy, halo, OH, hydroxyalkyl, alkoxyalkyl, aryl-heterocyclic, alkylaryl, cycloalkylalkyl, heterocyclic-alkyl, alkoxy, haloalkoxy, NH2, alkylamino, dialkylamino, arylamino, diarylamino,

alkylarylamino, alkoxyhaloalkyl, haloalkoxy, sulfonic acid, sulfonic ester, alkylsulfonic acid, arylsulfonic acid, arylalkoxy, alkylthio, arylthio, cycloalkylthio, cycloalkenyl, CN, aminoalkyl, aminoaryl, aryl, arylalkyl, alkylaryl, carboxamido, alkylcarboxamido, arylcarboxamido, amidyl, carboxyl, carbamoyl, alkylcarboxylic acid, arylcarboxylic acid, alkylcarbonyl, arylcarbonyl, ester, carboxylic ester, alkylcarboxylic ester, arylcarboxylic ester, haloalkoxy, sulfonamido, alkylsulfonamido, arylsulfonamido, sulfonic ester, a urea, phosphoryl, nitro, -T-Q or -(C(Re)(Rf))k-T-Q; or

Re+Rf+attached C atoms = carbonyl, methanthial, heterocyclic, cycloalkyl or a bridged cycloalkyl;

k = 1-3;

T = a covalent bond, carbonyl, O, -S(O)o- or -N(Ra)Ri-;

o = 0-2;

Ra = a lone pair of electrons, H or alkyl;

Ri = H, alkyl, aryl, alkylcarboxylic acid, arylcarboxylic acid, alkylcarboxylic ester, arylcarboxylic ester, alkylcarboxamido, arylcarboxamido, alkylaryl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, sulfonamido, carboxamido, carboxylic ester, amino alkyl, amino aryl, -CH2-C(T-Q)(Re)(Rf) or -(N2O2)-M+;

M+ = an organic or inorganic cation;

provided that when Ri is -CH2-C(T-Q)(Re)(Rf) or -(N2O2) M+; or Re or Rf are T-Q or (C(Re)(Rf))k-T-Q, then T-Q can be H, alkyl, alkoxy, alkoxyalkyl, aminoalkyl, OH, heterocyclic or aryl; and provided that when X is -C(O)OD1 and D1 is K, then K is not alkyl or cycloalkyl mononitrate; benzoic acid substituted benzyloxy mononitrate; ethylene glycol mononitrate; polyethylene glycol mononitrate; the regioisomeric esters of glycerol dinitrate and oligomers as disclosed in WO9858910.

INDEPENDENT CLAIMS are included for the following:

(a) compositions and kits comprising (I) and at least 1 compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, and/or at least 1 vasoactive agent; and

(b) compositions and kits comprising at least 1 prostaglandin and at least 1 S-nitrosothiol compound, useful for treating sexual dysfunction, a cerebrovascular disorder, cardiovascular disorder, benign prostatic hyperplasia, organ transplants, glaucoma or peptic ulcer, or for inducing an abortion.

ACTIVITY - Vasotropic; Cerebroprotective; Cardiant; Cytostatic; Ophthalmological; Antiulcer; Gynecological; Relaxant.

MECHANISM OF ACTION - Smooth muscle relaxant; Nitric oxide donor; Endothelium-derived relaxing factor agonist.

USE - For treating or preventing sexual dysfunction in males or females, treating a cerebrovascular disorder, cardiovascular disorder, benign prostatic hyperplasia, organ transplants, glaucoma or peptic ulcer, or for inducing an abortion (all claimed).

ADVANTAGE - The combination of a prostaglandin and a S-nitrosothiol gives synergistic results.

Dwg.0/4

L25 ANSWER 45 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:355438 BIOSIS

DOCUMENT NUMBER: PREV200200355438

TITLE: Efficacy and safety of **tadalafil** in men with erectile dysfunction with and without hypertension.

AUTHOR(S): Padma-Nathan, H. (1); Brock, G.; McMahon, C.; Chen, K. K.; Anglin, G.; Costigan, T.; Shen, W.; Watkins, V.; Whitaker, J. S.

CORPORATE SOURCE: (1) Keck School of Medicine, University of Southern California, Beverly Hills, CA USA

SOURCE: American Journal of Hypertension, (April, 2002) Vol. 15, No. 4 Part 2, pp. 143A-144A. http://www.ajh-us.org. print. Meeting Info.: Seventeenth Annual Scientific Meeting of the American Society of Hypertension New York, N.Y., USA May 14-18, 2002 ISSN: 0895-7061.
DOCUMENT TYPE: Conference
LANGUAGE: English

L25 ANSWER 46 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:355428 BIOSIS
DOCUMENT NUMBER: PREV200200355428
TITLE: Blood pressure and cardiovascular effects of **tadalafil**, a new PDE5 inhibitor.
AUTHOR(S): Hutter, A. M. (1); Kloner, R. A.; Watkins, V.; Costigan, T.; Bedding, A.; Mitchell, M.; Emmick, J.
CORPORATE SOURCE: (1) Massachusetts General Hospital, Harvard Medical School, Boston, MA USA
SOURCE: American Journal of Hypertension, (April, 2002) Vol. 15, No. 4 Part 2, pp. 140A. http://www.ajh-us.org. print. Meeting Info.: Seventeenth Annual Scientific Meeting of the American Society of Hypertension New York, N.Y., USA May 14-18, 2002 ISSN: 0895-7061.
DOCUMENT TYPE: Conference
LANGUAGE: English

L25 ANSWER 47 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:449004 BIOSIS
DOCUMENT NUMBER: PREV200100449004
TITLE: CialisTM (**IC351**) as a treatment of erectile dysfunction in diabetic men.
AUTHOR(S): Saenz De Tejada, Inigo (1); Fredlund, Paul (1); Anglin, Greg (1); Pullman, Bill (1); Emmick, Jeff (1)
CORPORATE SOURCE: (1) Madrid Spain
SOURCE: Diabetes, (June, 2001) Vol. 50, No. Supplement 2, pp. A425. print. Meeting Info.: 61st Scientific Sessions of the American Diabetes Association Philadelphia, Pennsylvania, USA June 22-26, 2001 ISSN: 0012-1797.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 48 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:380171 BIOSIS
DOCUMENT NUMBER: PREV200100380171
TITLE: CialisTM (**IC351**) provides prompt response and extended period of responsiveness for the treatment of men with erectile dysfunction (ED.
AUTHOR(S): Padma-Nathan, Harin (1); Rosen, Raymond C.; Shabsigh, Ridwan; Saikali, Khalil; Watkins, Vish S.; Pullman, Bill
CORPORATE SOURCE: (1) Los Angeles, CA USA
SOURCE: Journal of Urology, (May, 2001) Vol. 165, No. 5 Supplement, pp. 224. print. Meeting Info.: Annual Meeting of the American Urological Association, Inc. Anaheim, California, USA June 02-07, 2001 ISSN: 0022-5347.
DOCUMENT TYPE: Conference
LANGUAGE: English

Prepared by Toby Port, STIC, Biotech Library 308-3534

SUMMARY LANGUAGE: English

L25 ANSWER 49 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:381536 BIOSIS
DOCUMENT NUMBER: PREV200100381536
TITLE: Cellular localisation of phosphodiesterase type 11 (PDE11) in human corpus cavernosum and the contribution of PDE11 inhibition on nerve-stimulated relaxation.
AUTHOR(S): Baxendale, Rhona W. (1); Wayman, Christopher P. (1); Turner, Leigh (1); Phillips, Stephen C. (1)
CORPORATE SOURCE: (1) Sandwich UK
SOURCE: Journal of Urology, (May, 2001) Vol. 165, No. 5 Supplement, pp. 223-224. print.
Meeting Info.: Annual Meeting of the American Urological Association, Inc. Anaheim, California, USA June 02-07, 2001
ISSN: 0022-5347.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 50 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:262700 BIOSIS
DOCUMENT NUMBER: PREV200100262700
TITLE: CialisTM (**IC351**): Effective and well-tolerated treatment for ED.
AUTHOR(S): Brock, G. (1); Iglesias, J.; Toulouse, K.; Ferguson, K.; Pullman, W.; Anglin, G.
CORPORATE SOURCE: (1) Univ W Ontario, London, ON Canada
SOURCE: Journal of Andrology, (May June, 2001) No. Supplement, pp. 185. print.
Meeting Info.: VIIth International Congress of Andrology Montreal, Canada June 15-19, 2001
ISSN: 0196-3635.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 51 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:389604 BIOSIS
DOCUMENT NUMBER: PREV200100389604
TITLE: Efficacy and safety of **IC351** treatment for ED.
AUTHOR(S): Brock, G. (1); Iglesias, J.; Toulouse, K.; Ferguson, K.; Pullman, W.; Anglin, G.
CORPORATE SOURCE: (1) Univ. of W. Ontario, London, ON Canada
SOURCE: European Urology, (March, 2001) Vol. 39, No. Suppl. 5, pp. 106. print.
Meeting Info.: XVIth Congress of the European Association of Urology Geneva, Switzerland April 07-10, 2001
ISSN: 0302-2838.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 52 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:391998 BIOSIS
DOCUMENT NUMBER: PREV200100391998
TITLE: **IC351** enhances NO-mediated relaxation of human arterial and trabecular penile smooth muscle.
AUTHOR(S): Angulo, J. (1); Gadau, M.; Fernandez, A.; Gabancho, S.; Cuevas, P.; Martins, T.; Florio, V.; Ferguson, K.; Saenz De Tejada, I.

CORPORATE SOURCE: (1) Hospital Ramon y Cajal, Madrid Spain
SOURCE: European Urology, (March, 2001) Vol. 39, No. Suppl. 5, pp. 106. print.
Meeting Info.: XVIth Congress of the European Association of Urology Geneva, Switzerland April 07-10, 2001
ISSN: 0302-2838.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 53 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:375151 BIOSIS
DOCUMENT NUMBER: PREV200100375151
TITLE: The effect of on-demand **IC351** treatment of erectile dysfunction in men with diabetes.
AUTHOR(S): Saenz De Tejada, Inigo (1); Emmick, J.; Anglin, G.; Fredlund, P.; Pullman, W.
CORPORATE SOURCE: (1) Hospital Ramon y Cajal, Madrid Spain
SOURCE: European Urology, (March, 2001) Vol. 39, No. Suppl. 5, pp. 16. print.
Meeting Info.: XVIth Congress of the European Association of Urology Geneva, Switzerland April 07-10, 2001
ISSN: 0302-2838.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 54 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:211709 BIOSIS
DOCUMENT NUMBER: PREV200000211709
TITLE: Daily and on-demand **IC351** treatment of erectile dysfunction.
AUTHOR(S): Giuliano, Francois (1); Porst, Hartmut; Padma-Nathan, Harin; Saoud, Jay; Ferguson, Kenneth; Whitaker, Steven; Pullman, William; Rosen, Raymond
CORPORATE SOURCE: (1) Bicetre France
SOURCE: Journal of Urology, (April, 2000) Vol. 163, No. 4 Suppl., pp. 201.
Meeting Info.: 95th Annual Meeting of the American Urological Association, Inc. Atlanta, Georgia, USA April 29, 2000-May 04, 1999
ISSN: 0022-5347.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 55 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:356087 BIOSIS
DOCUMENT NUMBER: PREV200000356087
TITLE: On-demand treatment of erectile dysfunction with **IC351**.
AUTHOR(S): Padma-Nathan, Harin (1); McMurray, James; Saoud, Jay; Ferguson, Kenneth; Pullman, William; Whitaker, Steven; Rosen, Raymond
CORPORATE SOURCE: (1) Male Clinic, University of Southern California, Santa Monica, CA USA
SOURCE: European Urology, (March, 2000) Vol. 37, No. Suppl. 2, pp. 80. print.
Meeting Info.: XVth Congress of the European Association of Urology Brussels, Belgium April 12-15, 2000
ISSN: 0302-2838.

Prepared by Toby Port, STIC, Biotech Library 308-3534

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 56 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:356088 BIOSIS
DOCUMENT NUMBER: PREV200000356088
TITLE: Daily **IC351** treatment of erectile dysfunction.
AUTHOR(S): Giuliano, Francois (1); Meuleman, Eric; Saoud, Jay; Ferguson, Kenneth; Whitaker, Steven; Porst, Hartmut
CORPORATE SOURCE: (1) Department of Urology, University Hospital of Bicetre, Le Kremlin France
SOURCE: European Urology, (March, 2000) Vol. 37, No. Suppl. 2, pp. 80. print.
Meeting Info.: XVth Congress of the European Association of Urology Brussels, Belgium April 12-15, 2000
ISSN: 0302-2838.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L25 ANSWER 57 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:160377 BIOSIS
DOCUMENT NUMBER: PREV199900160377
TITLE: Effects of **IC351** on erectile response to visual sexual stimulation.
AUTHOR(S): Meuleman, Eric; Nijeholt, Guus Lycklama A; Slob, Koos; Roeleveld; Damen, Lianne; Brazao, Gouveia De C.; Harin, Padma-Nathan; Rosen, Raymond
CORPORATE SOURCE: Nijmegen Netherlands
SOURCE: Journal of Urology, (April, 1999) Vol. 161, No. 4 SUPPL., pp. 212.
Meeting Info.: 94th Annual Meeting of the American Urological Association, Inc. Dallas, Texas, USA May 1-6, 1999 American Urological Association
. ISSN: 0022-5347.
DOCUMENT TYPE: Conference
LANGUAGE: English

L25 ANSWER 58 OF 58 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1980:167480 BIOSIS
DOCUMENT NUMBER: BA69:42476
TITLE: CYTO GENETIC STUDIES ON FISHES 2. KARYOTYPES OF 4 CARANGID FISHES.
AUTHOR(S): MUROFUSHI M; YOSIDA T H
CORPORATE SOURCE: LAB. BIOL., MISHIMA JR. COLL., NIHON UNIV., MISHIMA, TOKYO 411, JPN.
SOURCE: JPN J GENET, (1979) 54 (5), 367-370.
CODEN: IDZAAW. ISSN: 0021-504X.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB All Trachurus japonicus, Caranx equula, C. sexfasciatus and Alectis **cialis** all had a diploid chromosome number of 48. The karotype consisted of all acrocentric chromosomes (no. 1-24) in A. cilialis, but the largest chromosome pair no. 1 was subtelocentric in C. equula and C. sexfasciatus. In T. japonicus the karyotype was different from the other species by consisting of 15 biarmed chromosome pairs (no. 1-15) and 9 acrocentric pairs (no. 16-24). The sex chromosomes cannot be identified in any of the 4 spp. studied. The relationship between karyotype differentiation and species diversity of carangid fishes was discussed.

Prepared by Toby Port, STIC, Biotech Library 308-3534

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

4743 7590 08/30/2002

MARSHALL, GERSTEIN & BORUN
6300 SEARS TOWER
233 SOUTH WACKER
CHICAGO, IL 60606-6357

EXAMINER
COOK, REBECCA

ART UNIT	PAPER NUMBER
1614	5

DATE MAILED: 08/30/2002

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

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 10/031,556	Applicant(s) PULLMAN ET AL.	
	Examiner Rebecca Cook	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

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

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

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

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

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

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 9-12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Intended use does not lend patentability to a composition claim.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over 6,140,329.

'329 (column 3, lines 48-65, column 5, lines 60-65, claims 16-17) disclose the instant compound and a method of using it to treat sexual dysfunction. It further discloses oral administration and a dosage within the recited range. It also discloses that individual enantiomers may be prepared.

The instant claims differ over '329 in reciting a unit dosage composition and a specific enantiomer. However, once a method of using a composition is known it is with the skill of the artisan to determine the optimum route of administration. Furthermore, in the absence of a showing of unexpected results in Declaration form no unobviousness is seen in using a specific enantiomer.

Applicants are requested to identify any related applications in which there may be double patenting.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Cook whose telephone number is (703) 308-4724. The examiner can normally be reached on Monday through Thursday from 5:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

August 29, 2002

Notice of References Cited

Application/Control No.	Applicant(s)/Patent Under Reexamination	
10/031,556	PULLMAN ET AL.	
Examiner	Art Unit	Page 1 of 1
Rebecca Cook	1614	

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-6,140,329	10-2000	Daugan	514/250
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 29342/36206A	Serial No. 10/031,556
INFORMATION DISCLOSURE STATEMENT *(Use several sheets if necessary)*		Applicant William Ernest Pullman et al.	
		Filing Date 10/19/01	Group Unassigned

U.S. PATENT DOCUMENTS

*Examiner Initials		Document Number	Issue Date	Name	Class	Subclass	Filing Date If Appropriate
W		5,859,006	01/12/99	Daugan	514	249	

FOREIGN PATENT DOCUMENTS

*Examiner Initials		Document Number	Publication Date	Country	Class	Subclass	Translation Yes	Translation No
W		WO 95/19978	27.07.95	PCT	C07D	471/14		
W		WO 97/03675	06.02.97	PCT	A61K	31/495		
W		WO 99/59584	25.11.99	PCT	A61K	31/415		
		~~WO 00/20033~~	~~13.04.00~~	~~JP~~			Abstract only	

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

W		Israel, *The Pharmaceutical Journal, 261*, pp. 164-165 (1998).
W		Goldenberg, *Clinical Therapeutics, 20*, No. 6, pp. 1033-1048 (1998).
W		WPIDS AN 2000 - 339026, Furitsu et al, JP 11990276134, 9/1999, abstract.

EXAMINER	R Cook	DATE CONSIDERED	8/28/02

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Interview Summary	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Rebecca Cook*. (3)_____.

(2) *James Napoli*. (4)_____.

Date of Interview: *13 November 2002* .

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____ .

Claim(s) discussed: *claims pending* .

Identification of prior art discussed: *art of record* .

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Examiner will consider a showing of unexpected results to overcome the rejection under 35 U.S.C. 103(a)* .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i)☒ It is not necessary for applicant to provide a separate record of the substance of the interview(if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Rebecca Cook
Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check the appropriate box at the bottom of the Form which informs the applicant that the submission of a separate record of the substance of the interview as a supplement to the Form is not required.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

PATENT - FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: **WILLIAM ERNEST PULLMAN ET AL.**

Serial No.: 10/031,556

Filed: October 19, 2001

For: **UNIT DOSAGE FORM**

Attorney Docket No. 29342/36206A

Group Art Unit: 1614

Examiner: Rebecca Cook

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents Washington, D.C. 20231.

Dated: **February 6, 2003**

James J. Napoli
Registration No. 32,361
Attorney for Applicants

AMENDMENT "A"

Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action of August 30, 2002, please amend the above-identified application as follows. Reconsideration and allowance of the application are respectfully requested.

IN THE CLAIMS:

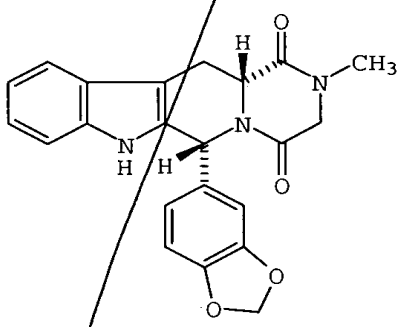
Cancel claims 9 and 10 without prejudice.

Amend claims 11, 12, and 13 as follows:

11. (Amended) The method of claim 13 wherein the sexual dysfunction is male erectile dysfunction.

12. (Amended) The method of claim 13 wherein the sexual dysfunction is female arousal disorder.

13. (Amended) A method of treating sexual dysfunction in a patient in need thereof comprising orally 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



REMARKS

Claims 1-17 are pending in the application. Claims 9 and 10 have been cancelled by this amendment. Therefore, claims 1-8 and 11-17 are at issue.

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."

The courteous interview granted to applicants' undersigned attorney by Examiner Cook on November 13, 2002 is hereby acknowledged with appreciation. During the interview, the outstanding Office Action, cited reference, claims on file, and proposed claim amendments were discussed in detail.

Claims 9-12 are objected to as being in improper form because an intended use in a dependent claim does not further limit an independent composition claim. In response, applicants have cancelled claims 9 and 10, and have amended claims 11 and 12 to recite a method and depend from independent claim 13. Accordingly, it is submitted that the objection to claims 11 and 12 has been overcome and should be withdrawn.

Claim 13 has been amended to recite that the unit dose is administered orally. Support for this amendment can be found in the specification at page 5, lines 16-25 and in Examples 5-7.

Claims 1-17 stand rejected under 35 U.S.C. §103 as being obvious over Daugan U.S. Patent No. 6,140,329 ('329). This rejection is based on the con-

tention that the '329 patent discloses the compound recited in the claims, use of the compound to treat sexual dysfunction, oral administration, and a dosage encompassing the recited dosage range. In view of the unexpected results demonstrated by the claimed compound at the claimed low dosage, it is submitted that this rejection is in error and should be withdrawn.

The present claims recite a unit dosage composition containing about 1 to about 20 mg of a specifically claimed compound and suitable for oral administration, and use of the unit dosage composition, up to a maximum dose of 20 mg per day, to treat sexual dysfunction. The oral unit dosage can be used to treat sexual dysfunction, including, for example, male erectile dysfunction (MED) and female arousal disorder (FAD), as recited in the claims. As discussed hereafter, the cited reference fails to teach or suggest an oral dosage form containing about 1 to about 20 mg of the claimed PDE5 inhibitor, or its use in a method of treating sexual dysfunction using a maximum total dose of about 20 mg per day.

It is submitted that the examiner's obviousness conclusion is incorrect because the '329 patent fails to teach or suggest a low oral dosage of the claimed PDE5 inhibitor to effectively treat sexual dysfunction. In addition, the presently claimed invention provides unexpected benefits and is a substantial advance in the art. In particular, the presently claimed invention (a) effectively treats sexual dysfunction using a low dose of a particular PDE5 inhibitor, (b) eliminates or reduces various adverse side effects associated with current PDE5 inhibitor therapy

used to treat sexual dysfunction, i.e., VIAGRA®, and (c) increases the population treatable for sexual dysfunction using a PDE5 inhibitor.

In particular, the '329 patent discloses a class of PDE inhibitors, including the compound recited in claim 1, useful in oral dosage forms over a range of 0.2-400 mg to treat sexual dysfunction. However, all examples in the '329 patent teach using 50 mg of active compound per dosage form. See columns 8-10 of the '329 patent. The '329 patent provides no teaching or suggestion of a preferred unit dose, except for the 50 mg dose in the examples. Thus, the lowest dose of PDE5 inhibitor embodied in the '329 patent in a unit dose composition is 50 mg of the active ingredient.

Therefore, although the '329 patent teaches a unit dosage range for the disclosed compounds of 0.2 to 400 mg, administered once or several times per day, the '329 patent does not teach or suggest a low *maximum* daily dose for effective treatment of sexual dysfunction. An important feature of the present invention is administration of an oral dose of the claimed unit dosage composition at 20 mg or less, per day, to treat sexual dysfunction (see claims 1 and 13). Such features are neither taught nor suggested in the '329 patent.

The '329 patent discloses thirteen specific compounds, and two preferred compounds, for the treatment of impotence. One of the preferred com-pounds, i.e., Example 1 (Compound A) of the '329 patent is Compound (I) recited in the present claims. The '329 patent also states that individual enantiomers can be prepared, as stated by the examiner.

Even though Compound (I) is disclosed as a *preferred* compound, the '329 patent contains no teaching or suggestion that Compound (I) was expected to successfully perform at a dosage less than 50 mg. The '329 patent merely teaches a broad dosage range for a class of compounds and for particular individual compounds. The only specific dosage disclosed in the '329 patent is 50 mg. Accordingly, insofar as the '329 patent does not disclose any dose below 50 mg, the '329 patent may be read to teach that a 50 mg dose is an effective dose of Compound (I). The lack of an example or any disclosure relating to a lower dose (i.e., less than 50 mg) for the *preferred* compounds of the '329 patent implies that it was not understood a lower dose of the claimed compound could effectively treat sexual dysfunction.

The '329 patent contains *no* disclosure that would lead a person skilled in the art to consider using the presently claimed low dose of Compound (I) with any reasonable expectation of successfully treating sexual dysfunction. In contrast, the present claims are enabled and supported by the clinical trials set forth in the specification. The specification, in Examples 6 and 7, clearly shows that a low dose of Compound (I) successfully treats sexual dysfunction *and* leads to a reduction or elimination of various adverse side effects.

In summary, there is no basis to contend that the presently claimed unit dosage composition or method would have been obvious from the '329 patent, which merely teaches a broad dosage range for a class of PDE5 inhibitors to treat sexual dysfunction. Furthermore,

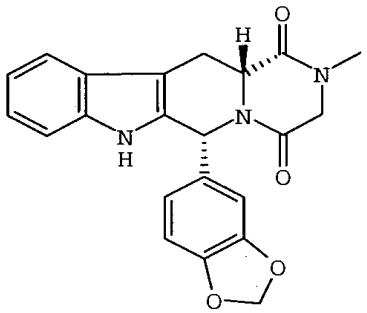
there is no incentive to provide a claimed unit dosage composition based on the examples of the '329 patent (limited to 50 mg dose).

The examiner states that no unexpected results are demonstrated for the claimed enantiomer. To the contrary, as discussed below, the claimed enantiomer possesses improved properties over its three stereoisomers.

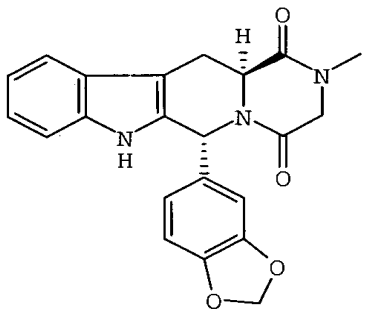
In particular, one important aspect of the present invention is the discovery of a bioavailable compound having a high potency and selectivity with respect to inhibiting PDE5. Bioavailability is one property that allows the PDE5 inhibitor to perform its intended function at a low dose. A high potency with respect to PDE5 is another property that allows administration of a low dose of the compound to inhibit PDE5. Selectivity is important because, coupled with bioavailability and potency, the PDE5 inhibitor can be administered at a sufficiently low dose such that it still can perform its intended function while other PDE enzymes are essentially unaffected. Undesired side effects attributed to inhibition of PDE enzymes other than PDE5, therefore, are avoided or reduced.

Compound (I) meets all of the above criteria of bioavailability, potency, and selectivity, which makes it useful in a low oral dosage form. In one series of tests, Compound (I) exhibited an IC_{50} vs. PDE5 of 2.5 nM, an IC_{50} vs. PDE6 of 3400 nM, and an IC_{50} vs. PDE1c of 10,000 nM. This series of tests show that Compound (I) is a potent inhibitor of PDE5 (low IC_{50}) and is selective in inhibiting PDE5 (PDE6/PDE5 IC_{50} ratio of 1360, and PDE1c/PDE5 IC_{50} ratio of 4,000).

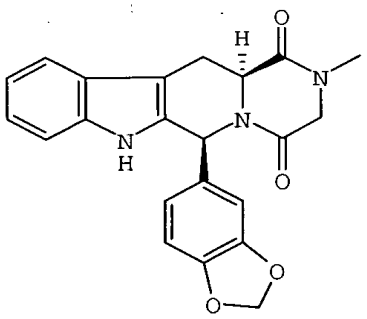
The discovery of a PDE5 inhibitor useful in a low unit dosage form to treat sexual dysfunction is not straightforward. In particular, not only do different compounds exhibit substantially different pharmacological properties, stereoisomers of a particular compound exhibit substantially different properties. For example, the following structures are Compound (I) (the (R,R) isomer) and its three stereoisomers.



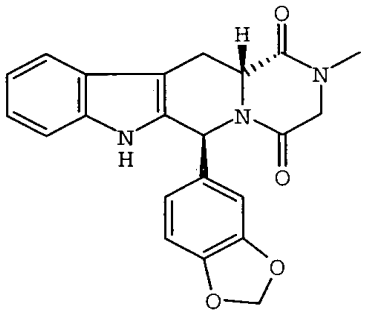
(R,R) isomer
Compound (I)



(R,S) isomer



(S,S) isomer



(S,R) isomer

In a comparative test, Compound (I) had an IC_{50} value vs. PDE5 of about 1 nM. The (R,S), (S,S), and (S,R) stereoisomers had IC_{50} values of vs. PDE5 14, 6,000, and 900 nM, respectively. The stereoisomers of a single compound, therefore, can have profoundly different properties with respect to PDE5 inhibition.

In addition, the presently claimed oral dosage form also satisfies a long-felt need in the art. A pharmaceutical product that provides a PDE5 inhibitor to treat erectile dysfunction is commercially available under the tradename VIAGRA®, which contains the active ingredient sildenafil citrate. VIAGRA® is sold as an article of manufacture including 25, 50, or 100 mg tablets of sildenafil citrate and a package insert. While VIAGRA® has obtained significant commercial

success, it has fallen short due to its adverse side effects, including facial flushing (i.e., 10% incidence rate). Adverse side effects also limit the use of sildenafil by patients suffering from vision abnormalities.

The VIAGRA® package insert (submitted concurrently with this amendment) teaches that sildenafil is a more potent inhibitor of PDE5 than other known phosphodiesterases. The IC_{50} for sildenafil against PDE5 has been reported as 3 nM (Boolel et al., *Int. J. of Impotence, 8*, pp. 47-52 (1996)). Sildenafil is described as having only a 10-fold IC_{50} selectivity for PDE5 versus PDE6. Its relative lack of selectivity for PDE6 is theorized to be the basis for abnormalities related to color vision, i.e., a blue-green vision, suffered by some users of VIAGRA® (3% incidence rate).

VIAGRA® also has a disadvantage in that ingestion of a meal prior to oral administration of a VIAGRA® tablet adversely effects the efficacy of the erectile dysfunction treatment. Sildenafil citrate also has a relatively short half-life after administration, such that sexual activity must be completed in about four hours after administration. Sexual activity, therefore, must be relatively carefully preplanned. In addition, the lowest labeled dose for VIAGRA® labeled is 25 mg, with the insert providing for dosages up to 100 mg. The greater the dose of sildenafil, the more probable an adverse side effect will occur. The VIAGRA® insert also has a warning that individuals suffering from a myocardial infarction within the last six months, or suffering from a retinal disease, such as retinitis pigmentosa, should not use

the product. Thus, even with the availability of VIAGRA®, there remains a need to identify improved PDE5 inhibitor pharmaceutical products that are useful in the treatment of sexual dysfunction.

A unit dosage composition containing Compound (I) is in the final approval stages at the Food and Drug Administration. After approval, which may occur in the second half of 2003, the unit dosage form containing Compound (I), also known as tadalafil, will be marketed under the tradename CIALIS®. CIALIS® will be in direct competition with VIAGRA®. As discussed hereafter, CIALIS® (i.e., a unit dosage composition of the present invention) overcomes some of the disadvantages associated with VIAGRA®, and provides an unexpected improvement in the art.

Applicants have discovered that the compound recited in independent claims 1 and 13 can be administered in a unit dosage composition containing about 1 to about 20 mg of the compound to provide an effective sexual dysfunction treatment, while reducing or eliminating various adverse side effects associated with VIAGRA®. The present invention is based on detailed experiments and clinical trials, and the unexpected discovery that various side effects previously believed attributable to PDE5 inhibition can be reduced to clinically insignificant levels by the selection of (a) a particular PDE5 inhibitor *and* (b) a particular low unit dosage. This unexpected discovery led to the development of a unit dosage composition incorporating about 1 to about 20 mg of Compound (I) that, when orally administered, effectively treats sexual dysfunction and eliminates or reduces various undesirable side

effects previously believed attributable to PDE5 inhibition, and, therefore, unavoidable. These adverse effects include facial flushing and vision abnormalities.

When administered in about 1 to about 20 mg unit dosage forms, the minimal effect of Compound (I) on PDE6 allows the treatment of sexual dysfunction in individuals who also may be suffering from a retinal disease, like diabetic retinopathy or retinitis pigmentosa. Such individuals previously shunned PDE5 inhibitor treatment for sexual dysfunctions because of warning on the VIAGRA® label, for example. Additional individuals that previously were excluded from, or shunned, PDE5 inhibitor treatment include those having suffered a myocardial infarction three to six months prior to the onset of PDE5 inhibitor therapy and those suffering from class 1 congestive heart failure. The present invention allows these individuals to use a PDE5 inhibitor to treat sexual dysfunction. The package insert for VIAGRA® warns such patients to avoid using sildenafil.

Clinical studies have shown that a presently claimed unit dosage composition is an effective product having a reduced tendency to cause flushing or visual abnormalities in susceptible individuals. See Examples 5-7, at pages 26-30 of the specification wherein using the claimed unit dosage composition also reported incidence of flushing below 2%. This incidence rate of flushing demonstrates marked improvement over VIAGRA®, i.e., 10% flushing incidence rate.

In particular, Example 6 shows that 5 to 20 mg doses of Compound (I) are efficacious, with less

than a 1% incidence of flushing and no reports of vision abnormalities. In contrast, the minimum labeled dose of sildenafil citrate is 25 mg, which has a 10% incidence of flushing. Example 7 shows that doses of Compound (I) less than 25 mg administered not more than once every twenty-four hours, produced a significant improvement in sexual performance relative to a placebo.

The incidence of adverse side effects attributed to administration of Compound (I) is set forth at page 32 of the specification. This table shows a lower incidence rate of various adverse side effects compared to the adverse events reported in the VIAGRA® insert, at page 15.

Examples 6 and 7 of the specification show that a unit dose containing about 1 to about 20 mg of Compound (I), administered up to a maximum of 20 mg per 24-hour period, effectively treats sexual dysfunction and reduces or eliminates the occurrence of various adverse side effects. Importantly, no vision abnormalities were reported, and flushing was essentially eliminated, when a unit dose composition of the present invention was administered. It is unexpected that Compound (I) is efficacious at about 1 to 20 mg dosage forms *and* reduces or eliminates various adverse side effects. In contrast, the labeled 25 to 100 mg dose of sildenafil citrate required to treat sexual dysfunctions results in increased adverse events.

The present invention, therefore, is an improvement over the only commercial PDE5 inhibitor treatment for sexual dysfunction, i.e., VIAGRA®. VIAGRA® must be administered orally in a dose of at

least 25 mg (the lowest labeled dosage), and can be administered up to 100 mg. Administration of sildenafil citrate also leads to various adverse side effects, as indicated in the VIAGRA® insert submitted concurrently with this amendment as Exhibit A. In addition, particular individuals are precluded from using sildenafil, as noted in the warnings and contraindications present on the VIAGRA® insert. The present invention reduces or eliminates some of these adverse side effects, and allows more individuals to use PDE5 inhibitor therapy to treat sexual dysfunction.

The present invention also provides an oral PDE5 inhibitor treatment for sexual dysfunction that previously was unavailable to a portion of the population. In particular, the present invention provides a PDE5 inhibitor treatment for sexual dysfunction to persons who could not, or preferred not to, undergo the treatment. Persons prone to flushing and vision abnormalities now can more freely use a PDE5 inhibitor treatment and have little to no concern with respect to these adverse effects. In addition, persons who were precluded from PDE5 inhibitor treatment now have an available treatment, e.g., persons suffering from a retinal disease, suffering from class 1 congestive heart failure, or having a myocardial infarction 3 to 6 months prior to onset of PDE5 inhibitor treatment.

In addition to a decrease in adverse side effects, a present unit dosage composition improves the spontaneity of sexual relations. First, ingesting a meal prior to administration of a claimed unit dose does *not* adversely affect the efficacy of Compound (I). Users of the present oral unit dosage composition,

therefore, are free to practice a more normal lifestyle without a reduction in treatment efficacy. Second, Compound (I) has a longer effective half-life than sildenafil after ingestion. Users of the present oral unit dosage composition, therefore, have a longer time frame in which to engage in sexual relations.

A person skilled in the art would not have been motivated from the '329 patent to provide a unit dose composition as recited in the present claims with any expectation that the unit dosage composition would provide such unexpected results in the treatment of sexual dysfunction. From a reading of the '329 patent, it would have been expected that a dose *greater* than 20 mg of Compound (I) is needed to treat sexual dysfunction effectively, i.e., about 50 mg. Additional unexpected benefits of the present invention are the improvements demonstrated by a claimed unit dosage composition over commercially available VIAGRA®. The present invention, therefore, not only is nonobvious over the '329 patent, but also satisfies unmet needs in the art.

In summary, the presently claimed invention would not have been obvious over the '329 patent, and the invention satisfies a long-felt need in the art. All examples in the '329 patent teach a 50 mg dose of the active compound. The cited art absolutely fails to suggest that a low dose of any PDE5 inhibitor, let alone the specific PDE5 inhibitor recited in claims 1 and 13, can be used to successfully treat sexual dysfunction, while eliminating or reducing various adverse side effects associated with the current PDE5 inhibitor treatment for sexual dysfunction.

The present invention is not directed to optimizing the dosage of PDE5 inhibitor or the route of administration, but is directed to the discovery of an oral dosage composition containing about 1 to about 20 mg of a specific PDE5 inhibitor that effectively treats sexual dysfunction. The reduced PDE5 inhibitor dosage not only performs its intended function, but reduces or eliminates various adverse effects associated with administration of sildenafil citrate, and allows a previously precluded segment of the population to undergo PDE5 inhibitor therapy to treat sexual dysfunction.

Applicants, therefore, have discovered a particular *low* unit dosage composition containing a particular PDE5 inhibitor that effectively treats ED, while avoiding or reducing various adverse side effects and expanding the population that is treatable using a PDE5 inhibitor. The '329 patent broadly discloses a dosage range for various PDE5 inhibitors, but fails to teach or suggest the specific dosage *and* the specific compound of the present invention that provides such new and unexpected benefits.

In view of all of the above, claims 1-8 and 11-17 would not have been obvious to a person skilled in the art, and the rejection of the pending claims under 35 U.S.C. §103 over the '329 patent should be withdrawn.

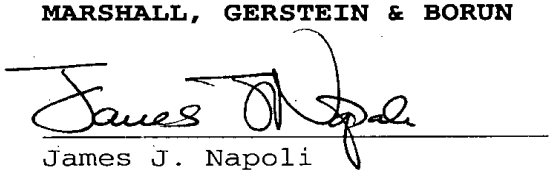
The examiner requested the identity of related applications in which double patenting may be an issue. In response, applicants bring U.S. Patent No. 6,451,807, U.S.S.N. 09/834,442, and U.S.S.N. 10/198,903 to the attention of the examiner for consideration.

It is submitted that the claims are now in 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 

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Chicago, Illinois
February 6, 2003

"Version With Markings to Show Changes Made"
(Pullman et al. U.S.S.N. 10/031,556)

IN THE CLAIMS:

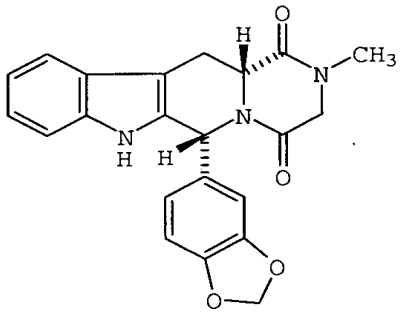
Claims 9 and 10 have been cancelled without prejudice.

Claims 11, 12, and 13 have been amended as follows:

11. (Amended) The [dosage form] method of claim [10] 13 wherein the sexual dysfunction is male erectile dysfunction.

12. (Amended) The [dosage form] method of claim [10] 13 wherein the sexual dysfunction is female arousal disorder.

13. (Amended) A method of treating sexual dysfunction in a patient in need thereof comprising orally 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



69-5485-00-6

U.S. Prescribing Information

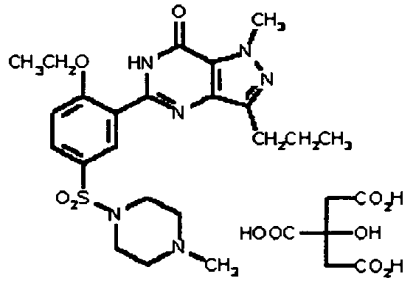
VIAGRA®
(sildenafil citrate)
Tablets

TOPICS

DESCRIPTION

VIAGRA®, an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate and has the following structural formula:



Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 666.7. VIAGRA (sildenafil citrate) is formulated as blue, film-coated rounded-diamond-shaped tablets equivalent to 25 mg, 50 mg and 100 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, lactose, triacetin, and FD & C Blue #2 aluminum lake.

TOP

CLINICAL PHARMACOLOGY

Mechanism of Action
The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect of nitric oxide (NO) by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation.

Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (>80-fold for PDE1, >1,000-fold for PDE2, PDE3, and PDE4). The approximately 4,000-fold selectivity for PDE5 versus PDE3 is important because that PDE is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina; this lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels (see **Pharmacodynamics**).

In addition to human corpus cavernosum smooth muscle, PDE5 is also found in lower concentrations in other tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet antiaggregatory activity of nitric oxide observed *in vitro*, an inhibition of platelet thrombus formation *in vivo* and peripheral arterial-venous dilatation *in vivo*.

Pharmacokinetics and Metabolism
VIAGRA is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. Its pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil. The concomitant use of potent cytochrome P450 3A4 inhibitors (e.g., erythromycin, ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION**). Both sildenafil and the metabolite have terminal half lives of about 4 hours.

Mean sildenafil plasma concentrations measured after the administration of a single oral dose of 100 mg to healthy male volunteers is depicted below:

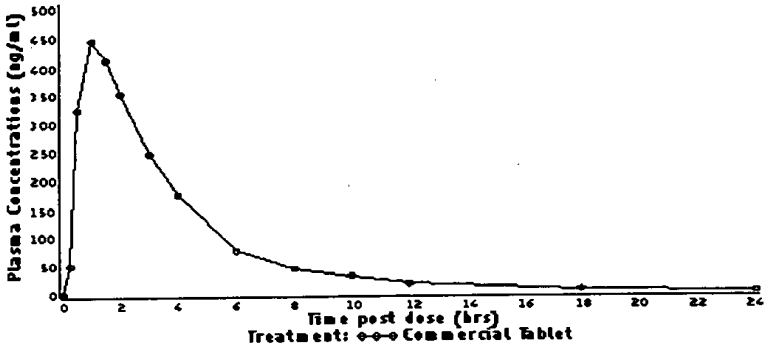


Figure 1: Mean Sildenafil Plasma Concentrations
in Healthy Male Volunteers.

Absorption and Distribution: VIAGRA is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When VIAGRA is taken with a high fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Based upon measurements of sildenafil in semen of healthy volunteers 90 minutes after dosing, less than 0.001% of the administered dose may appear in the semen of patients.

Metabolism and Excretion: Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects.

After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose). Similar values for pharmacokinetic parameters were seen in normal volunteers and in the patient population, using a population pharmacokinetic approach.

Pharmacokinetics in Special Populations
Geriatrics: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

Renal Insufficiency: In volunteers with mild (CLcr=50-80 mL/min) and moderate

(CLcr=30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of VIAGRA (50 mg) were not altered. In volunteers with severe (CLcr=<30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment.

Hepatic Insufficiency: In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment.

Therefore, age >65, hepatic impairment and severe renal impairment are associated with increased plasma levels of sildenafil. A starting oral dose of 25 mg should be considered in those patients (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics

Effects of VIAGRA on Erectile Response: In eight double-blind, placebo-controlled crossover studies of patients with either organic or psychogenic erectile dysfunction, sexual stimulation resulted in improved erections, as assessed by an objective measurement of hardness and duration of erections (RigiScan®), after VIAGRA administration compared with placebo. Most studies assessed the efficacy of VIAGRA approximately 60 minutes post dose. The erectile response, as assessed by RigiScan®, generally increased with increasing sildenafil dose and plasma concentration. The time course of effect was examined in one study, showing an effect for up to 4 hours but the response was diminished compared to 2 hours.

Effects of VIAGRA on Blood Pressure: Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease of 8.4/5.5 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different than placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg of VIAGRA, therefore the effects are not related to dose or plasma levels. Larger effects were recorded among patients receiving concomitant nitrates (see **CONTRAINDICATIONS**).

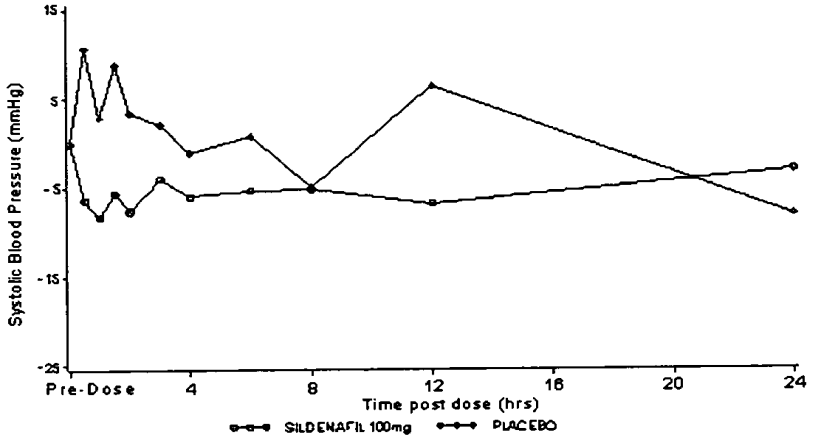


Figure 2: Mean Change from Baseline in Sitting Systolic Blood Pressure, Healthy Volunteers.

Effects of VIAGRA n Cardiac Parameters: Single oral doses of sildenafil up to 100 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

Studies have produced relevant data on the effects of VIAGRA on cardiac output. In one small, open-label, uncontrolled, pilot study, eight patients with stable ischemic heart disease underwent Swan-Ganz catheterization. A total dose of 40 mg sildenafil was administered by four intravenous infusions.

The results from this pilot study are shown in Table 1; the mean resting systolic and diastolic blood pressures decreased by 7% and 10% compared to baseline in these patients. Mean resting values for right atrial pressure, pulmonary artery pressure, pulmonary artery occluded pressure and cardiac output decreased by 28%, 28%, 20% and 7% respectively. Even though this total dosage produced plasma sildenafil concentrations which were approximately 2 to 5 times higher than the mean maximum plasma concentrations following a single oral dose of 100 mg in healthy male volunteers, the hemodynamic response to exercise was preserved in these patients.

TABLE 1. HEMODYNAMIC DATA IN PATIENTS WITH STABLE ISCHEMIC HEART DISEASE AFTER IV ADMINISTRATION OF 40 MG SILDENAFIL

Means ± SD	At rest				After 4 minutes of exercise			
	n	Baseline (B2)	n	Sildenafil (D1)	n	Baseline	n	Sildenafil
PAOP (mmHg)	8	8.1 ± 5.1	8	6.5 ± 4.3	8	36.0 ± 13.7	8	27.8 ± 15.3
Mean PAP (mmHg)	8	16.7 ± 4	8	12.1 ± 3.9	8	39.4 ± 12.9	8	31.7 ± 13.2
Mean RAP (mmHg)	7	5.7 ± 3.7	8	4.1 ± 3.7	-	-	-	-
Systolic SAP (mmHg)	8	150.4 ± 12.4	8	140.6 ± 16.5	8	199.5 ± 37.4	8	187.8 ± 30.0
Diastolic SAP (mmHg)	8	73.6 ± 7.8	8	65.9 ± 10	8	84.6 ± 9.7	8	79.5 ± 9.4
Cardiac output (L/min)	8	5.6 ± 0.9	8	5.2 ± 1.1	8	11.5 ± 2.4	8	10.2 ± 3.5
Heart rate (bpm)	8	67 ± 11.1	8	66.9 ± 12	8	101.9 ± 11.6	8	99.0 ± 20.4

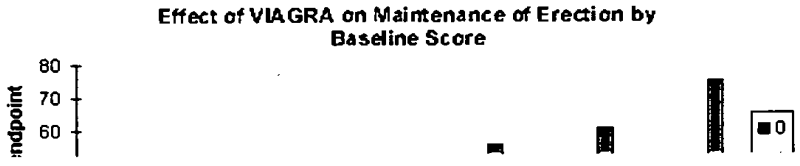
Effects of VIAGRA on Vision: At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of VIAGRA on visual acuity, intraocular pressure, or pupillometry.

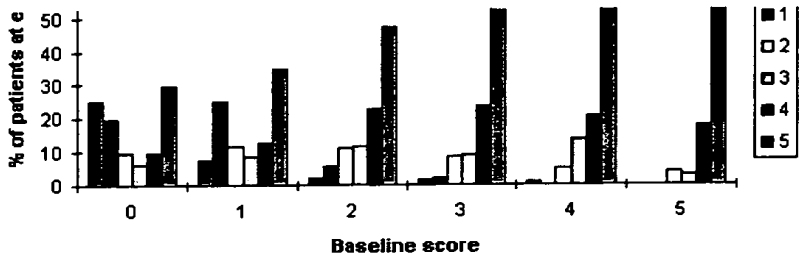
Clinical Studies

In clinical studies, VIAGRA was assessed for its effect on the ability of men with erectile dysfunction (ED) to engage in sexual activity and in many cases specifically on the ability to achieve and maintain an erection sufficient for satisfactory sexual activity. VIAGRA was evaluated primarily at doses of 25 mg, 50 mg and 100 mg in 21 randomized, double-blind, placebo-controlled trials of up to 6 months in duration, using a variety of study designs (fixed dose, titration, parallel, crossover). VIAGRA was administered to more than 3,000 patients aged 19 to 87 years, with ED of various etiologies (organic, psychogenic, mixed) with a mean duration of 5 years. VIAGRA demonstrated statistically significant improvement compared to placebo in all 21 studies. The studies that established benefit demonstrated improvements in success rates for sexual intercourse compared with placebo.

The effectiveness of VIAGRA was evaluated in most studies using several assessment instruments. The primary measure in the principal studies was a sexual function questionnaire (the International Index of Erectile Function - IIEF) administered during a 4-week treatment-free run-in period, at baseline, at follow-up visits, and at the end of double-blind, placebo-controlled, at-home treatment. Two of the questions from the IIEF served as primary study endpoints; categorical responses were elicited to questions about (1) the ability to achieve erections sufficient for sexual intercourse and (2) the maintenance of erections after penetration. The patient addressed both questions at the final visit for the last 4 weeks of the study. The possible categorical responses to these questions were (0) no attempted intercourse, (1) never or almost never, (2) a few times, (3) sometimes, (4) most times, and (5) almost always or always. Also collected as part of the IIEF was information about other aspects of sexual function, including information on erectile function, orgasm, desire, satisfaction with intercourse, and overall sexual satisfaction. Sexual function data were also recorded by patients in a daily diary. In addition, patients were asked a global efficacy question and an optional partner questionnaire was administered.

The effect on one of the major end points, maintenance of erections after penetration, is shown in Figure 3, for the pooled results of 5 fixed-dose, dose-response studies of greater than one month duration, showing response according to baseline function. Results with all doses have been pooled, but scores showed greater improvement at the 50 and 100 mg doses than at 25 mg. The pattern of responses was similar for the other principal question, the ability to achieve an erection sufficient for intercourse. The titration studies, in which most patients received 100 mg, showed similar results. Figure 3 shows that regardless of the baseline levels of function, subsequent function in patients treated with VIAGRA was better than that seen in patients treated with placebo. At the same time, on-treatment function was better in treated patients who were less impaired at baseline.





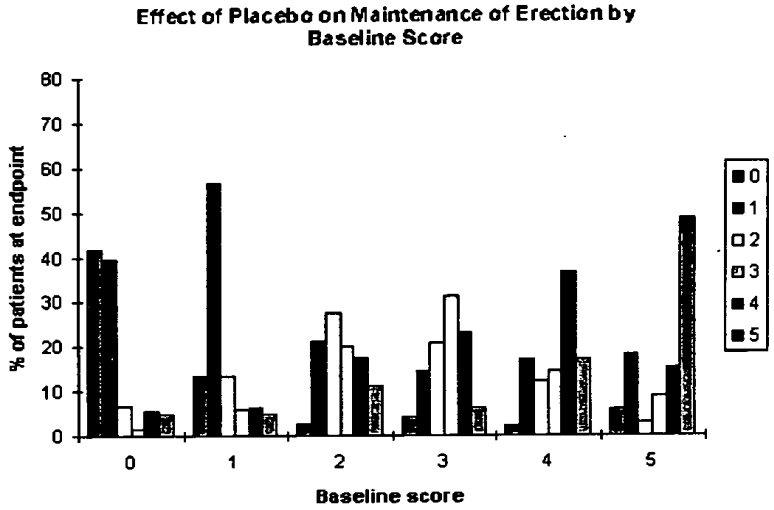


Figure 3. Effect of VIAGRA and Placebo on Maintenance of Erection by Baseline Score.

The frequency of patients reporting improvement of erections in response to a global question in four of the randomized, double-blind, parallel, placebo-controlled fixed dose studies (1797 patients) of 12 to 24 weeks duration is shown in Figure 4. These patients had erectile dysfunction at baseline that was characterized by median categorical scores of 2 (a few times) on principal IIEF questions. Erectile dysfunction was attributed to organic (58%; generally not characterized, but including diabetes and excluding spinal cord injury), psychogenic (17%), or mixed (24%) etiologies. Sixty-three percent, 74%, and 82% of the patients on 25 mg, 50 mg and 100 mg of VIAGRA, respectively, reported an improvement in their erections, compared to 24% on placebo. In the titration studies (n=644) (with most patients eventually receiving 100 mg), results were similar.

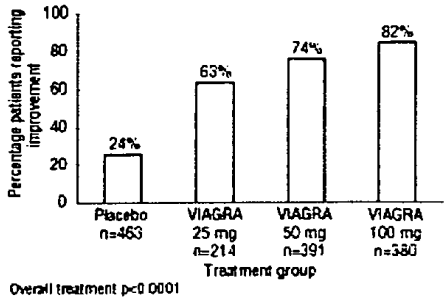


Figure 4. Percentage of Patients Reporting an Improvement in Erections.

The patients in studies had varying degrees of ED. One-third to one-half of the subjects in these studies reported successful intercourse at least once during a 4-week, treatment-free run-in period.

In many of the studies, of both fixed dose and titration designs, daily diaries were kept by patients. In these studies, involving about 1600 patients, analyses of patient diaries showed no effect of VIAGRA on rates of attempted intercourse (about 2 per week), but there was clear treatment-related improvement in sexual function: per patient weekly success rates averaged 1.3 on 50-100 mg of VIAGRA vs 0.4 on placebo; similarly, group mean success rates (total successes divided by total attempts) were about 66% on VIAGRA vs about 20% on placebo.

During 3 to 6 months of double-blind treatment or longer-term (1 year), open-label studies, few patients withdrew from active treatment for any reason, including lack of effectiveness. At the end of the long-term study, 88% of patients reported that VIAGRA improved their erections.

Men with untreated ED had relatively low baseline scores for all aspects of sexual function measured (again using a 5-point scale) in the IIEF. VIAGRA improved these aspects of sexual function: frequency, firmness and maintenance of erections; frequency of orgasm; frequency and level of desire; frequency, satisfaction and enjoyment of intercourse; and overall relationship satisfaction.

One randomized, double-blind, flexible-dose, placebo-controlled study included only patients with erectile dysfunction attributed to complications of diabetes mellitus (n=268). As in the other titration studies, patients were started on 50 mg and allowed to adjust the dose up to 100 mg or down to 25 mg of VIAGRA; all patients, however, were receiving 50 mg or 100 mg at the end of the study. There were highly statistically significant improvements on the two principal IIEF questions (frequency of successful penetration during sexual activity and maintenance of erections after penetration) on VIAGRA compared to placebo. On a global improvement question, 57% of VIAGRA patients reported improved erections versus 10% on placebo. Diary data indicated that on VIAGRA, 48% of intercourse attempts were successful versus 12% on placebo.

One randomized, double-blind, placebo-controlled, crossover, flexible-dose (up to 100 mg) study of patients with erectile dysfunction resulting from spinal cord injury (n=178) was conducted. The changes from baseline in scoring on the two end point questions (frequency of successful penetration during sexual activity and maintenance of erections after penetration) were highly statistically significantly in favor of VIAGRA. On a global improvement question, 83% of patients reported improved erections on VIAGRA versus 12% on placebo. Diary data indicated that on VIAGRA, 59% of attempts at sexual intercourse were successful compared to 13% on placebo.

Across all trials, VIAGRA improved the erections of 43% of radical prostatectomy patients compared to 15% on placebo.

Subgroup analyses of responses to a global improvement question in patients with psychogenic etiology in two fixed-dose studies (total n=179) and two titration studies (total n=149) showed 84% of VIAGRA patients reported improvement in erections compared with 26% of placebo. The changes from baseline in scoring on the two end point questions (frequency of successful penetration during sexual activity and maintenance of erections after penetration) were highly statistically significantly in favor of VIAGRA. Diary data in two of the studies (n=178) showed rates of successful intercourse per attempt of 70% for VIAGRA and 29% for placebo.

A review of population subgroups demonstrated efficacy regardless of baseline severity, etiology, race and age. VIAGRA was effective in a broad range of ED patients, including those with a history of coronary artery disease, hypertension, other cardiac disease, peripheral vascular disease, diabetes mellitus, depression, coronary artery bypass graft (CABG), radical prostatectomy, transurethral resection of the prostate (TURP) and spinal cord injury, and in patients taking antidepressants/antipsychotics and antihypertensives/diuretics.

Analysis of the safety database showed no apparent difference in the side effect profile in patients taking VIAGRA with and without antihypertensive medication. This analysis was performed retrospectively, and was not powered to detect any pre-specified difference in adverse reactions.

TOP

INDICATION AND USAGE

VIAGRA is indicated for the treatment of erectile dysfunction.

TOP

CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see **CLINICAL PHARMACOLOGY**), VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

After patients have taken VIAGRA, it is unknown when nitrates, if necessary, can be safely administered. Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post dose are approximately 2 ng/mL (compared to peak plasma levels of approximately 440 ng/mL) (see **CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism**). In the following patients: age >65, hepatic impairment (e.g., cirrhosis), severe renal impairment (e.g., creatinine clearance <30 mL/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely coadministered at this time point.

VIAGRA is contraindicated in patients with a known hypersensitivity to any component of the tablet.

TOP

WARNINGS

There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including VIAGRA, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

VIAGRA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mmHg), (see **CLINICAL PHARMACOLOGY: Pharmacodynamics**). While this normally would be expected to be of little consequence in most patients, prior to prescribing VIAGRA, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

There is no controlled clinical data on the safety or efficacy of VIAGRA in the following groups; if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (BP <90/50) or hypertension (BP >170/110);
- Patients with cardiac failure or coronary artery disease causing unstable angina;
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of

VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

The concomitant administration of the protease inhibitor ritonavir substantially increases serum concentrations of sildenafil (**11-fold increase in AUC**). If VIAGRA is prescribed to patients taking ritonavir, caution should be used. Data from subjects exposed to high systemic levels of sildenafil are limited. Visual disturbances occurred more commonly at higher levels of sildenafil exposure. Decreased blood pressure, syncope, and prolonged erection were reported in some healthy volunteers exposed to high doses of sildenafil (200-800 mg). To decrease the chance of adverse events in patients taking ritonavir, a decrease in sildenafil dosage is recommended (see **Drug Interactions, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

TOP

PRECAUTIONS

General

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

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

Patients on multiple antihypertensive medications were included in the pivotal clinical trials for VIAGRA. In a separate drug interaction study, when amlodipine, 5 mg or 10 mg, and VIAGRA, 100 mg were orally administered concomitantly to hypertensive patients mean additional blood pressure reduction of 8 mmHg systolic and 7 mmHg diastolic were noted (see **Drug Interactions**). Controlled studies of drug interactions between VIAGRA and other antihypertensive medications have not been performed.

The safety of VIAGRA is unknown in patients with bleeding disorders and patients with active peptic ulceration.

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

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

In humans, VIAGRA has no effect on bleeding time when taken alone or with aspirin. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and VIAGRA had an additive effect on bleeding time in the anesthetized

rabbit, but this interaction has not been studied in humans.

Information f r Patients
Physicians should discuss with patients the contraindication of VIAGRA with regular and/or intermittent use of organic nitrates.

Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors. Patients who experience symptoms (e.g., angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician.

Physicians should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

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

Drug Interactions
Effects of Other Drugs on VIAGRA
***In vitro* studies:** Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.

***In vivo* studies:** Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with VIAGRA (50 mg) to healthy volunteers.

When a single 100 mg dose of VIAGRA was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In addition, in a study performed in healthy male volunteers, coadministration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1200 mg tid) with VIAGRA (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. VIAGRA had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole or itraconazole would be expected to have still greater effects, and population data from patients in clinical trials did indicate a reduction in sildenafil clearance when it was coadministered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine) (see **DOSAGE AND ADMINISTRATION**).

In another study in healthy male volunteers, coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with VIAGRA (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil

C_{max} and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. VIAGRA had no effect on ritonavir pharmacokinetics (see **DOSAGE AND ADMINISTRATION**).

Although the interaction between other protease inhibitors and sildenafil has not been studied, their concomitant use is expected to increase sildenafil levels.

It can be expected that concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of VIAGRA.

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

Effects of VIAGRA on Other Drugs
***In vitro* studies:** Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

***In vivo* studies:** When VIAGRA 100 mg oral was coadministered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

VIAGRA (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

In a study of healthy male volunteers, sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUCs) for unbound sildenafil and its major

metabolite of 29- and 42-times, for male and female rats, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg. Sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m^2 basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males, a dose producing an AUC value of more than 25 times the human male AUC.

There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers.

Pregnancy, Nursing Mothers and Pediatric Use
VIAGRA is not indicated for use in newborns, children, or women.

Pregnancy Category B. No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the MRHD on a mg/m^2 basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well-controlled studies of sildenafil in pregnant women.

Geriatric Use: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil (see **CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations**). Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered (see **DOSAGE AND ADMINISTRATION**).

TOP

ADVERSE REACTIONS

PRE-MARKETING EXPERIENCE:
VIAGRA was administered to over 3700 patients (aged 19-87 years) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for VIAGRA (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

In trials of all designs, adverse events reported by patients receiving VIAGRA were generally similar. In fixed-dose studies, the incidence of some adverse events increased

with dose. The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies.

When VIAGRA was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the following adverse events were reported:

TABLE 2. ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA N=734	PLACEBO N=725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal Congestion	4%	2%
Urinary Tract Infection	3%	2%
Abnormal Vision*	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

*Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

Other adverse reactions occurred at a rate of >2%, but equally common on placebo: respiratory tract infection, back pain, flu syndrome, and arthralgia.

In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

Body as a whole: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

Digestive: vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

Hemic and Lymphatic: anemia and leukopenia.

Metabolic and Nutritional: thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.

Respiratory: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and Appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special Senses: mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, deafness, ear pain, eye hemorrhage, cataract, dry eyes.

Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

POST-MARKETING EXPERIENCE:
Cardiovascular
Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack and hypertension, have been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of VIAGRA without sexual activity. Others were reported to have occurred hours to days after the use of VIAGRA and sexual activity. It is not possible to determine whether these events are related directly to VIAGRA, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see **WARNINGS** for further important cardiovascular information).

Other events
Other events reported post-marketing to have been observed in temporal association with VIAGRA and not listed in the pre-marketing adverse reactions section above include:

Nervous: seizure and anxiety.

Urogenital: prolonged erection, priapism (see **WARNINGS**) and hematuria.

Ocular: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular edema.

TOP

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

TOP

DOSAGE AND ADMINISTRATION

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, VIAGRA may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.

The following factors are associated with increased plasma levels of sildenafil: age >65 (40% increase in AUC), hepatic impairment (e.g., cirrhosis, 80%), severe renal impairment (creatinine clearance <30 mL/min, 100%), and concomitant use of potent cytochrome P450 3A4 inhibitors [ketoconazole, itraconazole, erythromycin (182%), saquinavir (210%)]. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.

Ritonavir greatly increased the systemic level of sildenafil in a study of healthy, non-HIV infected volunteers (11-fold increase in AUC, see **Drug Interactions**.) Based on these pharmacokinetic data, it is recommended not to exceed a maximum single dose of 25 mg of VIAGRA in a 48 hour period.

VIAGRA was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated.

TOP

HOW SUPPLIED

VIAGRA® (sildenafil citrate) is supplied as blue, film-coated, rounded-diamond-shaped tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as follows:

	25 mg	50 mg	100 mg
Obverse	VGR25	VGR50	VGR100
Reverse	PFIZER	PFIZER	PFIZER
Bottle of 30	NDC-0069-4200-30	NDC-0069-4210-30	NDC-0069-4220-30
Bottle of 100	N/A	NDC-0069-4210-66	NDC-0069-4220-66

Recommended Storage: Store at controlled room temperature, 15° to 30°C (59° to 86° F).

Rx only

Distributed by
Pfizer Labs
Division of Pfizer Inc. NY, NY 10017

Printed in U.S.A.
Revised January 2000

69-5485-00-6

#9 #9 JRP 4/10/03

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents Washington, D.C. 20231.
WILLIAM ERNEST PULLMAN ET AL.	
Serial No.: 10/031,556	
Filed: October 19, 2001	
For: **UNIT DOSAGE FORM**	
Attorney Docket No. 29342/36206A	Dated: **February 6, 2003**
Group Art Unit: 1614	
Examiner: Rebecca Cook	James J. Napoli Registration No. 32,361 Attorney for Applicants

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to their duty of disclosure under 37 C.F.R. §1.56, applicants hereby bring to the examiner's attention information 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, applicants enclose a completed Form PTO-1449 identifying the possibly pertinent information, and a copy of the information.

This Supplemental Information Disclosure Statement is submitted more than three months after the filing date of the above-identified application, and after the mailing date of a first Office Action on the

merits in the above-identified application. This Supplemental Information Disclosure Statement, however, is filed before the mailing date of a final action and before the mailing date of a notice of allowance. Therefore, under 37 C.F.R. §1.97(c), this Supplemental Information Disclosure Statement shall be considered by the Patent Office because it is accompanied by the fee set forth in 37 C.F.R. §1.17(p).

The Commissioner 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.

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
February 6, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): WILLIAM ERNEST PULLMAN ET AL.	Title: UNIT DOSAGE FORM
Serial No: 10/031,556	Group Art Unit: 1614
Filed: October 19, 2001	Examiner: Rebecca Cook
Attorney Docket No. 29342/36206A	

AMENDMENT TRANSMITTAL WITH PETITION FOR EXTENSION OF TIME

Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment for the above application.

CERTIFICATE OF MAILING (37 CFR 1.8)

I hereby certify that this paper and the documents referred to as enclosed therewith are being deposited with the United States Postal Service as first class mail, postage prepaid, on February 6, 2003 in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231.

02/10/2003 WABDELR1 00000099 10031556
02 FC:1253 930.00 OP

James J. Napoli

1. **Small Entity Status**

☐ Verified statement(s) claiming small entity status is(are) attached.

☐ Small entity status has been established and is still effective.

☒ Has not been established.

2. **Extension of Time**

☒ This is a petition for an extension of time under 37 CFR 1.136 for the total number of months checked below:

EXTENSION (Months)	FEE FOR LARGE ENTITY		FEE FOR SMALL ENTITY	
One Month		$110.00		$55.00
Two Months		$410.00		$205.00
Three Months	x	$930.00		$465.00
Four Months		$1,450.00		$725.00
Fifth Month		$1,970.00		$985.00

If an additional Extension of Time is required, please consider this a petition therefor.

Extension Fee: $930.00

☐ An extension for month(s) has already been secured and the fee paid therefor of $ is deducted from the total fee due for the total months of extension now requested.

Deduction: $0.00

Extension Fee Due With This Request $930.00

3. Fee for Claims

☐ The fee for additional claims [(37 CFR 1.16(b)-(d)] has been calculated as shown below:

					SMALL ENTITY		OTHER THAN A SMALL ENTITY	
	Claims Remaining After Amendment	Highest No. Previously Paid For		Present Extra	Rate	Additional Fee	Rate	Additional Fee
TOTAL	20	MINUS	20	=0	X 9=	$	X18=	$0
INDEP.	1	MINUS	3	=0	X42=	$	X84=	$0
First Presentation of Multiple Dependent Claim					+140=	$	+280=	
TOTAL ADDITIONAL FEE					$		**OR**	$0

4. Method of Payment of Fees

☒ Attached is a check in the amount of: $930.00

☐ Charge Deposit Account No. 13-2855
in the amount of: $

A copy of this Transmittal is enclosed.

5. Deposit Account and Refund Authorization

The Commissioner is hereby authorized to charge any deficiency in the amount enclosed or any additional fees which may be required during the pendency of this application under 37 CFR 1.16 or 1.17 to Deposit Account No. 13-2855. A copy of this Transmittal is enclosed.

Please refund any overpayment to Marshall, Gerstein & Borun at the address below.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6357
(312) 474-6300

By: James J. Napoli
Reg. No: 32,361

February 6, 2003

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

4743 7590 04/11/2003

MARSHALL, GERSTEIN & BORUN
6300 SEARS TOWER
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CHICAGO, IL 60606-6357

EXAMINER	
COOK, REBECCA	
ART UNIT	PAPER NUMBER
1614	10

DATE MAILED: 04/11/2003

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

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

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

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

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

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

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

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

In view of the amendments to the claims the earlier objection is overcome.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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

Claims 1—8, 11-17 are again rejected under 35 U.S.C. 103(a) as being unpatentable over 6,140,329 for the reasons given in Paper No. 5. Applicants argue that '329 fails to suggest the instant low oral dosage, since the examples are to 50 mg. This is not persuasive, In '329, column 3, line 51 discloses a dosage range that includes the instant dose and column 10, lines 1-3 recites that other doses [than 50 mg] may be prepared. Applicant also argues that the instant examples show a low incidence of side effects as compared to adverse events reported in the VIAGRA (sildenafil) insert. This is not persuasive, since the compound of '329 is the instant compound and is not sildenafil.

In the absence of a showing of unexpected results no unobviousness is seen in using 20 mg of the instant enantiomer over 50 mg of the compound of '329.

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

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Cook whose telephone number is (703) 308-4724. The examiner can normally be reached on Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

REBECCA COOK
PRIMARY EXAMINER
GROUP ~~1200~~ 1614

April 9, 2003

Form 1449PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/031,556
Filing Date	October 19, 2001
First Named Inventor	William E. Pullman et al.
Group Art Unit	1614
Examiner Name	Rebecca Cook
Attorney Docket Number	29342/36206A

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document	Publication Date MM-DD-YYYY

OTHER PRIOR ART – NONPATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published.
RC		NDA 20-895 (New Drug Application) Sildenafil for Male Impotence, pages 99-103 and 183-187, 22 January 1998, author unknown.

Examiner Signature	RCook	Date Considered	4/9/03

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1614

PATENT--FEE

8/6/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

WILLIAM ERNEST PULLMAN ET AL.

Serial No.: 10/031,556

Filed: October 19, 2001

For: **UNIT DOSAGE FORM**

Attorney Docket No. 29342/36206A

Group Art Unit: 1614

Examiner: Rebecca Cook

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: July 24, 2003

James J. Napoli
Registration No. 32,361
Attorney for Applicants

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Pursuant to their duty of disclosure under 37 C.F.R. §1.56, applicants hereby bring to the examiner's attention a patent 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, applicants enclose a completed Form PTO-1449 listing the possibly pertinent patent and a copy of the patent.

This Supplemental Information Disclosure Statement is submitted more than three months after the filing date of the above-identified application, which is presently under final rejection. Therefore, under 37 C.F.R. §1.97(d), this Supplemental Information Disclosure

Statement shall be considered by the Patent Office because: (1) each item of information contained in this Supplemental Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Supplemental Information Disclosure Statement (37 C.F.R. §1.97(e)(1)), and (2) the fee set forth in 37 C.F.R. §1.17(p) is submitted herewith.

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 Hungarian Search Report, and an English language translation, is enclosed for the convenience of the examiner and to complete the file. Please not that references cited in a previous Information Disclosure Statement are not cited herein. In addition, the enclosed U.S. Patent No. 6,451,807 corresponds to HU P0001632A.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

By _____
James J. Napoli
Registration No. 32,361

July 24, 2003

RESPONSE UNDER 37 C.F.R. 116
EXPEDITED PROCEDURE
EXAMINING ART UNIT 1614

PATENT--NO FEE

#15/C
JRP
9/11/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	CERTIFICATE OF TRANSMISSION
WILLIAM ERNEST PULLMAN ET AL.	I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office to Examiner R. Cook at facsimile number (703) 746-5317 on September 9, 2003
Serial No.: 10/031,556	
Filed: October 19, 2001	
For: UNIT DOSAGE FORM	
Attorney Docket No. 29342/36206A	
Group Art Unit: 1614	
Examiner: Rebecca Cook	James J. Napoli Registration No. 32,361 Attorney for Applicants

AMENDMENT "B" AFTER FINAL UNDER 37 C.F.R. §1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In response to the Office Action of April 11, 2003, please amend the above-identified application as follows. Reconsideration and allowance of the application are respectfully requested.

PTO/SB/17 (08-03)
Approved for use through 07/31/2006, OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,160.00

Complete if Known	
Application Number	10/031,556-Conf. #06526
Filing Date	October 19, 2001
First Named Inventor	William E. Pullman
Examiner Name	R. Cook
Art Unit	1614
Attorney Docket No.	29342/36206A

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 13-2855

Deposit Account Name: MARSHALL, GERSTEIN & BORUN LLP

The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☐ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	
1002	330	2002	165	Design filing fee	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		-** =		x		=	
Independent Claims		-** =		x		=	
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	410.00
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37CFR 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	750.00
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify)					

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 1,160.00

SUBMITTED BY

(Complete *(if applicable)*)

Name (Print/Type)	James J. Napoli	Registration No. (Attorney/Agent)	32,361	Telephone	(312) 474-6614
Signature	James J. Napoli			Date	September 9, 2003

MARSHALL, GERSTEIN & BORUN LLP
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(312) 474-6300
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September 9, 2003

FACSIMILE TRANSMISSION SHEET

TO	Examiner R. Cook
COMPANY	U.S. Patent & Trademark Office
FAX NO.	703 746 5317
PHONE NO.	

FROM: James J. Napoli		**EXTENSION:**	811
PAGES (INCLUDING THIS PAGE):	16	**CLIENT NO:**	29342
		MATTER NO:	36206A
PLEASE CONFIRM RECEIPT:	No	**COUNTRY CODE:**	US

MESSAGE:

Please contact if you do not receive all of the pages in good condition.

****

Received from < 312 474 0448 > at 9/9/03 1:46:55 PM [Eastern Daylight Time]

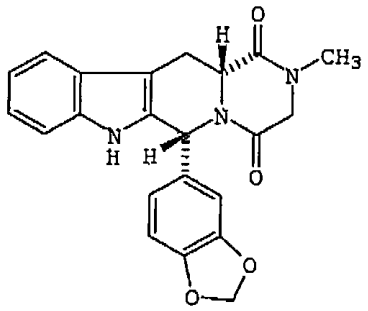
IN THE CLAIMS:

1.-10. (Cancelled)

11. (Previously amended) The method of claim 13 wherein the sexual dysfunction is male erectile dysfunction.

12. (Previously amended) The method of claim 13 wherein the sexual dysfunction is female arousal disorder.

13. (Previously amended) A method of treating sexual dysfunction in a patient in need thereof comprising orally 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. (Original) The method of claim 13 wherein the unit dose contains about 2 to about 20 mg of the compound.

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

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

17. (Original) 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.-19. (Cancelled)

20. (New) The method of claim 13 wherein the unit dose contains about 2.5 mg of the compound.

21. (New) The method of claim 20 wherein the unit dose is administered once per day.

22. (New) The method of claim 15 wherein the unit dose is administered once per day.

23. (New) The method of claim 13 wherein the compound is administered as a free drug.

REMARKS

Claims 1-8 and 11-17 are pending in the application. Claims 1-8 have been cancelled by this amendment. New claims 20-23 have been added to the application. Therefore, claims 11-17 and 20-23 are at issue.

This amendment is submitted in accordance with 37 C.F.R. §1.116(a) and §1.116(b) in order to present the rejected claims in a better form for allowance or appeal. The amendment is necessary to eliminate a rejection under 35 U.S.C. §103. This amendment was not presented earlier because applicants believed and still believe that the amendment mailed February 6, 2003 overcame the rejection under 35 U.S.C. §103. The amendment should be entered because (a) it places the application in better form for allowance or appeal, and the amendment does not require further searching or present any new issues, and (b) a Request for Continued Examination (RCE) is submitted concurrently with this amendment.

The courteous telephonic interview granted to applicants' undersigned attorney by Examiner Cook on August 26, 2003 is hereby acknowledged with appreciation. During the interview, the outstanding Office Action, cited reference, and claims on file were discussed in detail.

New claims 20-23 have been added to the application. These new claims are fully supported in the application as originally filed, see, for example, original, and now-cancelled, claim 4 and claim 16, and

the specification at page 7, lines 26-28, and page 9, line 32 through page 10, line 3.

Claims 1-8 and 11-17 stand rejected under 35 U.S.C. §103 as being obvious over Daugan U.S. Patent No. 6,140,329 ('329). This rejection is based on the contention that the '329 patent discloses the compound recited in the claims, use of the compound to treat sexual dysfunction, oral administration, and a dosage encompassing the recited dosage range. In view of the unexpected results demonstrated by the claimed compound at the claimed low dosage (i.e., about 1 to about 20 mg) and claimed low maximum total daily dose (i.e., maximum 20 mg/day), it is submitted that this rejection is in error and should be withdrawn.

In particular, composition claims 1-8 have been cancelled without prejudice. In view of the telephonic interview, these composition claims have been cancelled to facilitate prosecution, and not because of questions relating to patentability. The composition claims will be pursued in a continuation application.

It is submitted that for the reasons set forth in Amendment "A" mailed February 6, 2003 and incorporated herein by reference, and because of the new and unexpected results achieved by the present invention, it is submitted that method claims 11-17 and new claims 20-23 would not have been obvious to a person skilled in the art, and the rejection of the pending claims under 35 U.S.C. §103 over the '329 patent should be withdrawn.

The present claims recite a method of treating sexual dysfunction in a patient in need thereof by

the oral administration of a unit dosage composition containing about 1 to about 20 mg of a specifically claimed compound, up to a maximum dose of 20 mg per day. The method can be used to treat sexual dysfunction, including, for example, male erectile dysfunction (MED) and female arousal disorder (FAD), as recited in the claims. As discussed in Amendment "A" and hereafter, the cited reference fails to teach or suggest a method of treating sexual dysfunction using about 1 to about 20 mg of the claimed PDE5 inhibitor, up to a maximum total dose of about 20 mg per day.

It is submitted that the examiner's obviousness conclusion is incorrect because the '329 patent fails to teach or suggest a low oral dosage of the claimed PDE5 inhibitor to effectively treat sexual dysfunction. In addition, the presently claimed invention provides unexpected benefits and is a substantial advance in the art. In particular, the presently claimed invention (a) effectively treats sexual dysfunction using a low dose of a particular PDE5 inhibitor, (b) eliminates or reduces various adverse side effects associated with current PDE5 inhibitor therapy used to treat sexual dysfunction, i.e., VIAGRA®, and (c) increases the population treatable for sexual dysfunction using a PDE5 inhibitor.

In particular, the '329 patent discloses a class of PDE inhibitors, including the compound recited in claim 13, useful in oral dosage forms over a range of 0.2-400 mg to treat sexual dysfunction. However, all examples in the '329 patent teach using 50 mg of active compound per dosage form. See columns 8-10 of

the '329 patent. The '329 patent provides no teaching or suggestion of a preferred unit dose, except for the 50 mg dose in the examples. Thus, the lowest dose of PDE5 inhibitor embodied in the '329 patent in a unit dose composition is 50 mg of the active ingredient.

Although column 10, lines 1-3 of the '329 patent states that "other doses may be prepared," this teaching does not address the dosage needed for an effective treatment of sexual dysfunction. This statement in the '329 patent merely is directed to teaching those skilled in the art how to make a different unit dose. This teaching of the '329 patent, however, fails to instruct whether the 50 mg dose should be increase or decreased.

Therefore, although the '329 patent teaches a unit dosage range for the disclosed compounds of 0.2 to 400 mg, administered once or several times per day, the '329 patent does not teach or suggest a low *maximum* daily dose for effective treatment of sexual dysfunction. An important feature of the present invention is administration of an oral dose of the claimed unit dosage composition at 20 mg or less, per day, to treat sexual dysfunction (see claim 13). Such a feature is neither taught nor suggested in the '329 patent.

The '329 patent discloses thirteen specific compounds, and two preferred compounds, for the treatment of impotence. One of the preferred com-pounds, i.e., Example 1 (Compound A) of the '329 patent is Compound (I) recited in the present claims.

Even though Compound (I) is disclosed as a *preferred* compound, the '329 patent contains no teach-

ing or suggestion that Compound (I) can be expected to successfully perform at a dosage less than 50 mg. The '329 patent merely teaches a broad dosage range for a class of compounds and for particular individual compounds. The only specific dosage disclosed in the '329 patent, and particularly for Compound (I), is 50 mg.

Accordingly, insofar as the '329 patent does not disclose any dose below 50 mg for Compound (I) or any other compound, the '329 patent can be read to teach that a 50 mg dose is an effective dose of Compound (I). The disclosure at column 10, lines 1-3 of the '329 patent does not alter this teaching for the reasons set forth above. The lack of an example or any specific disclosure relating to a lower dose (i.e., less than 50 mg) for the *preferred* compounds of the '329 patent implies that it was not understood a lower dose of the claimed compound could effectively treat sexual dysfunction.

The '329 patent contains *no* disclosure that would lead a person skilled in the art to consider using the presently claimed low unit dose and maximum daily dose of Compound (I) with any reasonable expectation of successfully treating sexual dysfunction. In contrast, the present claims are enabled and supported by the clinical trials set forth in the specification. The specification, in Examples 6 and 7, clearly shows that a low dose of Compound (I) successfully treats sexual dysfunction *and* leads to a reduction or elimination of various adverse side effects.

In summary, there is no basis to contend that the presently claimed unit dosage composition or method

would have been obvious from the '329 patent, which merely teaches a broad dosage range for a class of PDE5 inhibitors to treat sexual dysfunction. Furthermore, there is no incentive to provide a claimed unit dosage composition based on the examples of the '329 patent (limited to 50 mg dose).

The examiner states that no unexpected results are demonstrated for the claimed enantiomer. To the contrary, as discussed in Amendment "A" at pages 7-9, and incorporated herein by reference, the claimed enantiomer possesses improved properties over its three stereoisomers.

In addition, the presently claimed invention satisfies a long-felt need in the art. A unit dosage composition containing Compound (I) is in the final approval stages at the Food and Drug Administration. After approval, which is expected in late 2003, the unit dosage form containing Compound (I), also known as tadalafil, will be marketed under the tradename CIALIS®. CIALIS® will be in direct competition with VIAGRA®. CIALIS® (i.e., a unit dosage composition of the present invention) overcomes some of the disadvantages associated with prior PDE5 inhibitor treatments of sexual dysfunction, e.g., VIAGRA®, and provides an unexpected improvement in the art.

Applicants have discovered that the compound recited in independent claim 13 can be administered in a unit dosage composition containing about 1 to about 20 mg of the compound, up to a maximum dose of 20 mg/day, to provide an effective method of treating sexual dysfunction, while reducing or eliminating

various adverse side effects associated with VIAGRA®. This aspect of the present invention is discussed in Amendment "A," pages 11-14, incorporated herein by reference.

For example, clinical studies have shown that a method of treating sexual dysfunction utilizing a presently claimed unit dosage effectively reduces flushing or visual abnormalities in susceptible individuals. See Examples 5-7, at pages 26-30 of the specification, wherein administration of the claimed unit dosage composition reported incidence of flushing below 2%. This incidence rate of flushing demonstrates marked improvement over VIAGRA®, i.e., 10% flushing incidence rate reported on the VIAGRA® label.

A person skilled in the art would not have been motivated from the '329 patent to provide a method as recited in the present claims with any expectation that claimed unit dosage and low maximum daily dose would provide such unexpected results in the treatment of sexual dysfunction. From a reading of the '329 patent, it would have been expected that a dose *greater* than a daily 20 mg maximum dose of Compound (I) is needed to treat sexual dysfunction effectively, i.e., about 50 mg. Additional unexpected benefits of the present invention are the improvements demonstrated by the claimed over present-day, commercially available PDE5 inhibitor treatment for sexual dysfunction. The present invention, therefore, not only is nonobvious over the '329 patent, but also satisfies long-felt and unmet needs in the art.

In summary, the presently claimed invention would not have been obvious over the '329 patent, and the invention satisfies a long-felt need in the art. All examples in the '329 patent teach a 50 mg dose of the active compound. The cited art absolutely fails to suggest that a low dose of any PDE5 inhibitor, let alone the specific PDE5 inhibitor recited in claim 13, can be used in a method to successfully treat sexual dysfunction, while eliminating or reducing various adverse side effects associated with the current PDE5 inhibitor treatment for sexual dysfunction.

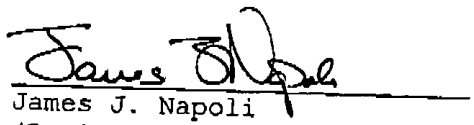
Applicants, therefore, have discovered a method of treating sexual dysfunction wherein a particular *low* unit dosage composition containing a particular PDE5 inhibitor effectively treats sexual dysfunction using a 20 mg/day maximum dose, while avoiding or reducing various adverse side effects. The '329 patent broadly discloses a dosage range for various PDE5 inhibitors, but fails to teach or suggest the specific unit dosage, maximum daily dosage, *and* the specific compound of the present invention that provides such new and unexpected benefits.

It is submitted, therefore, that the claims are now in 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 LLP

By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
September 9, 2003

PTO/SB/30 (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

#14
JRP
9/11/03

Request For Continued Examination (RCE) Transmittal

Address to:
MS RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/031,556-Conf. #06526
Filing Date	October 19, 2001
First Named Inventor	William E. Pullman
Art Unit	1614
Examiner Name	R. Cook
Attorney Docket No.	29342/36206A

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
   - a. [ ] Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. [ ] Other _____
   - b. [X] Enclosed
     - i. [X] Amendment/Reply
     - ii. [ ] Affidavit(s)/Declaration(s)
     - iii. [ ] Information Disclosure Statement (IDS)
     - iv. [ ] Other _____
2. Miscellaneous
   - a. [ ] Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. [ ] Other _____
3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   - a. [X] The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 13-2855
     - i. [X] RCE fee required under 37 CFR 1.17(e)
     - ii. [X] Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. [ ] Other _____
   - b. [ ] Check in the amount of $ _____ enclosed
   - c. [ ] Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print/Type)	James J. Napoli	Registration No. (Attorney/Agent)	32,361
Signature	James J. Napoli	Date	September 9, 2003

09/11/2003 FPATTERS 00000001 132855 10031556
01 FC:1801 750.00 DA

PTO/SB/22 (08-03)
Approved for use through 7/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

#13 JKP 9/11/03

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket No. (Optional) 29342/36206A

In re Application of	William E. Pullman, et al.		
Application Number	10/031,556-Conf. #06526	Filed	October 19, 2001
For:	UNIT DOSAGE FORM		
Art Unit	1614	Examiner	R. Cook

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

☐	One month (37 CFR 1.17(a)(1))	$
☒	Two months (37 CFR 1.17(a)(2))	$ 410.00
☐	Three months (37 CFR 1.17(a)(3))	$
☐	Four months (37 CFR 1.17(a)(4))	$
☐	Five months (37 CFR 1.17(a)(5))	$

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $ _____ .

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 13-2855 .

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☐ attorney or agent of record. Registration Number _____

☒ attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a) 32,361

September 9, 2003
Date


Signature

(312) 474-6614
Telephone Number

James J. Napoli
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below

☐ Total of 1 forms are submitted.

09/11/2003 FPATTERS 00000002 132855 10031556
01 FC:1252 410.00 DA

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

4743 7590 09/17/2003

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER
COOK, REBECCA

ART UNIT	PAPER NUMBER
1614	16

DATE MAILED: 09/17/2003

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

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

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

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-17 and 20-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-17 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

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

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

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

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 9, 2003 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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

Claims 11-17, 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over 6,140,329 (Daugan) for the reasons given in Paper No. 5. Daugan (col. 1, compound (I), col. 3, lines 48-65, col. 5, lines 60-65,col. 7, Ex. 1, Compound A, claims 16-17) disclose the instant compound and a method of using it to treat sexual dysfunction. It further discloses oral administration and a dosage within the recited range.

Applicants continue to argue that the instant compound has reduced side effects when compared with Viagra. This is not persuasive, since the two compounds are structurally different.

Applicants continue to argue that Daugan fails to suggest the instant low dose, since the examples are to 50 mg. This is not persuasive. Daugan discloses (column 3, lines 50-52) a dose ranging from 0.5-800 mg, which includes the instant 1-20 mg. In the absence of a showing of unexpected results comparing the disclosed 50 mg dose of Daugan with upper dosage range of 20 mg of instant claim 13 no unobviousness is seen in the dosage range of the instant claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-17, 20-23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim1-7 of U.S. Patent No. 6,451,807. Although the conflicting claims are not identical, they are not patentably distinct from each other because the comprising language of the instant claims would include treating sexual dysfunction in a patient suffering from a retinal disease or the heart conditions recited in claim 4 of '807. Furthermore, claim 7 of '807 teaches the compound of the instant method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Cook whose telephone number is (703) 308-4724. The examiner can normally be reached on Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Rebecca Cook

REBECCA COOK
PRIMARY EXAMINER
GROUP ~~1200~~ 1614

September 16, 2003

Form 1449PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/031,556
Filing Date	October 19, 2001
First Named Inventor	Pullman et al.
Group Art Unit	1614
Examiner Name	Rebecca Cook
Attorney Docket Number	29342/36206A

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY
RC		6,451,807	09/17/02

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document	Publication Date MM-DD-YYYY

OTHER PRIOR ART – NONPATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published.

Examiner Signature	RCook	Date Considered	9/13/03

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Interview Summary	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Rebecca Cook*. (3)_____.

(2) *James Napoli*. (4)_____.

Date of Interview: *26 August 2003*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *pending claims*.

Identification of prior art discussed: *art of record*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Examiner informed attorney for applicants that the composition claims are not allowable and that a showing of unexpected results commensurate in scope with the claims is required to overcome the prior art for the method claims*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Rebecca Cook
Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Intervi w Summary	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Rebecca Cook*. (3) *Soonhee Jang*.

(2) *James Napoli*. (4)_____.

Date of Interview: *10 December 2003*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☒ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *Calims pending*.

Identification of prior art discussed: *art of record*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Attorneys for applicants will submit a Declaration under 37 CFR 1.132 which shows unexpected reduction of side effect at 20 mg when compared to the 50 mg dosage disclosed in Daugan. They will also submit a Terminal Disclaimer over 6,451,807. Examiner will consider a showing of unexpected results favorably.*

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

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Rebecca Cook

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PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

WILLIAM ERNEST PULLMAN ET AL.

Serial No.: 10/031,556

Filed: October 19, 2001

For: **UNIT DOSAGE FORM**

Attorney Docket No. 29342/36206A

Group Art Unit: 1614

Examiner: Rebecca Cook

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dated: January 12, 2004

James J. Napoli
Registration No. 32,361
Attorney for Applicants

RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

This is a response to the Office Action of September 17, 2003. Reconsideration and allowance of the application are respectfully requested.

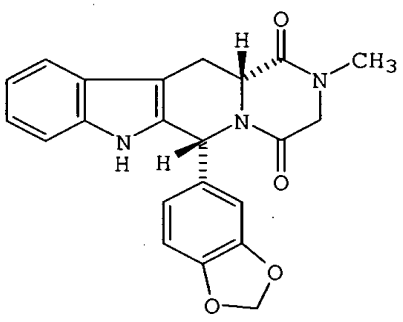
The following sets forth the current status of the claims:

1.-10. (Cancelled)

11. (Previously amended) The method of claim 13 wherein the sexual dysfunction is male erectile dysfunction.

12. (Previously amended) The method of claim 13 wherein the sexual dysfunction is female arousal disorder.

13. (Previously amended) A method of treating sexual dysfunction in a patient in need thereof comprising orally 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. (Original) The method of claim 13 wherein the unit dose contains about 2 to about 20 mg of the compound.

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

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

17. (Original) 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.-19. (Cancelled)

20. (Previously presented) The method of claim 13 wherein the unit dose contains about 2.5 mg of the compound.

21. (Previously presented) The method of claim 20 wherein the unit dose is administered once per day.

22. (Previously presented) The method of claim 15 wherein the unit dose is administered once per day.

23. (Previously presented) The method of claim 13 wherein the compound is administered as a free drug.

24. (New) The method of claim 13 wherein the unit dose contains about 20 mg of the compound.

Claims 11-17 and 20-23 are pending in the application. New claim 24 has been added to the application. Therefore, claims 11-17 and 20-24 are at issue.

New claim 24 recites a unit dose of about 20 mg of Compound (I). Support for claim 24 can be found, for example, in claims 13 and 14.

The courteous interview granted to applicants' undersigned attorney and Soonhee Jang by Examiner Cook on December 10, 2003 is hereby acknowledged with appreciation. During the interview, the outstanding Office Action, cited reference, and claims on file were discussed in detail.

Claims 11-17 and 20-23 stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 6,451,807. In view of the terminal disclaimer filed concurrently with this response, it is submitted that this rejection has been overcome and should be withdrawn.

Claims 11-17 and 20-23 stand rejected under 35 U.S.C. §103 as being obvious over Daugan U.S. Patent No. 6,140,329 ('329). This rejection is based on the contention that the '329 patent discloses the compound recited in the claims, use of the compound to treat sexual dysfunction, oral administration, and a dosage encompassing the recited dosage range. For the reasons set forth herein, it is submitted that claims 11-17 and 20-24 would not have been obvious to a person skilled in the art under 35 U.S.C. §103 over the '329 patent.

The present claims recite a method of treating sexual dysfunction in a patient in need thereof by the oral administration of a unit dosage composition

containing about 1 to about 20 mg of Compound (I), up to a maximum dose of 20 mg per day. The method can be used to treat sexual dysfunction, including male erectile dysfunction (MED) and female arousal disorder (FAD), as recited in the claims. The '329 patent discloses the use of compounds A and B for treating sexual dysfunction over the broad range of 0.5-800 mg, and in tablet or capsule dosage forms over a range of 0.2-400 mg to treat sexual dysfunction (column 3, lines 48-55).

The unit dose range of 1-20 mg as claimed in independent claim 13 of the present application is important because at this dose range it has surprisingly low adverse side effects while still unexpectedly found to be efficacious. The present specification discloses clinical study results showing that a dose range of about 2 mg to 100 mg are efficacious (specification, page 31), but doses at a level greater than about 20 mg (e.g., 25 mg to 100 mg) result in unpleasant adverse events, such as headache, dyspepsia, and back pain (specification, page 30, lines 15-23 and page 32, lines 15-20). The present specification further discloses "even though efficacy in the treatment of ED was observed at 25 mg to 100 mg unit doses, the adverse events observed from 25 mg to 100 mg dose must be considered" (Example 7 of the specification shows that undesirable adverse events are dose related). Consequently, doses of Compound (I) above about 20 mg would have reduced tolerability because of an increased level of adverse events.

Although the '329 patent teaches a unit dosage range for the disclosed compounds of 0.2 to 400 mg, administered once or several times per day, the '329

patent does not teach or suggest a low *maximum* daily dose for effective treatment of sexual dysfunction. An important feature of the present invention is administration of an oral dose of the claimed unit dosage composition at about 20 mg or less, per day, to treat sexual dysfunction, while substantially reducing adverse events associated with this PDE5 inhibitor treatment.

The '329 patent does not suggest or forecast that a low unit dose of about 1 to about 20 mg of Compound (I) would exhibit unexpected efficacy *and* at the same time unexpectedly reduce the number of adverse events. The '329 patent discloses a broad dose range of 0.2-400 mg in tablets or capsules, but this disclosure would not have *suggested* to one of ordinary skill in the art *at the time invention was made* that the low claimed dose range presently claimed would exhibit the unexpectedly surprising results of not only being efficacious, but also substantially reducing the number of adverse events as discussed above. The '329 patent broadly discloses a dosage range for various PDE5 inhibitors, but fails to teach or suggest the specific unit dosage, maximum daily dosage, *and* the specific compound of the present invention that provides such new and unexpected benefits. Although column 10, lines 1-3 of the '329 patent states that "other doses may be prepared," it provides largely or at best an illustrative purpose as to show those skilled in the art how to make a different formulation.

In addition to the above remarks, the Declaration of Gregory D. Sides, M.D. (Sides Declaration) submitted concurrently with this response, illustrates

and corroborates the new and unexpected results provided by the presently claimed invention, i.e., the discovery that the compound recited in independent claim 13 can be orally administered in one or more unit dose containing about 1 to about 20 mg of the compound, up to a maximum dose of 20 mg/day, to provide an effective method of treating sexual dysfunction, while substantially reducing various adverse events. The original signed copy of the Sides Declaration will be retained in applicants' file, but will be forwarded to the examiner upon request.

It is submitted that the claims are in 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 LLP

By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
January 12, 2004

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:
WILLIAM ERNEST PULLMAN ET AL.
Serial No.: 10/031,556
Filed: October 19, 2001
For: UNIT DOSAGE FORM
Attorney Docket No. 29342/36206A
Group Art Unit: 1614
Examiner: Rebecca Cook

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to:
Commissioner for Patent
P.O. Box 1450
Alexandria, VA 22313-1450

James J. Napoli
Registration No. 32,361
Attorney for Applicants

DECLARATION OF DR. GREGORY D. SIDES, M.D., F.A.C.E.P., F.A.C.P.
UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

NOW COMES Dr. Gregory D. Sides, Declarant herein, and states as follows:

1. I presently hold the position of Medical Director, Primary Care Products, Cialis® Product Team at Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285.

2. My previous positions were:

Director, Bioproduct Medical, Eli Lilly and Company, Indianapolis, Indiana (Jan 2002 - Jan 2003)

Director of Operations, Global Clinical Research, Eli Lilly and Company, Indianapolis, Indiana (Feb 2001 - Jan 2002)

Acting Director, Cardiovascular Medical, Eli Lilly and Company, Indianapolis, Indiana (Jul 2000 - Feb 2001)

Senior Clinical Research Physician, Cardiovascular, Medical, Eli Lilly and Company, Indianapolis, Indiana (Jan 1999 - Jul 2000)

Clinical Research Physician, Cardiovascular Division, Eli Lilly and Company, Indianapolis, Indiana (Jul 1994 - Dec 1998)

Clinical Research Physician, Infectious Diseases Division, Eli Lilly and Company, Indianapolis, Indiana (Mar 1990 - Jul 1994)

Associate Clinical Research Physician, Infectious Diseases Division, Eli Lilly and Company, Indianapolis, Indiana (Feb 1988 - Mar 1990)

Partner, Kirtley, Paschall, Sides Emergency Physicians, Inc., Danville, Indiana (Nov 1984 - Mar 1988)

Hendricks Community Hospital, Danville, Indiana (Nov 1984 - Mar 1988)

Emergency Physician, Midwest Medical Management, Inc. Indianapolis, Indiana (Jul 1983 - Nov 1984)

3. I received a degree in Medicine from the Indiana University of Medicine, Indianapolis, Indiana in 1980. I received a B.S. in Chemistry, Magna Cum Laude, from Indiana State University, Terre Haute, Indiana in 1977.

I completed an Internship and Residency in Internal Medicine at Methodist Hospital, Indianapolis, Indiana (1980-1983)

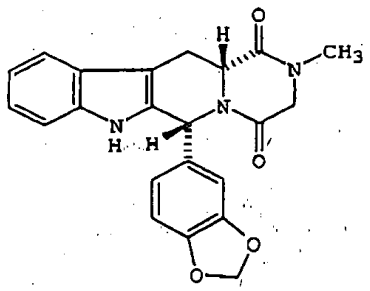
I am board certified in Internal Medicine and Emergency Medicine: Board of Certification: Diplomate, American Board of Internal Medicine, September 14, 1983 (#092096); Diplomate: American Board of Emergency Medicine, March 17, 1989 - December 31, 1999, Recertification, December 24, 1998 - December 31, 2008 (#870725)

4. I have practiced medicine for twenty three (23) years, conducted research, published about 28 articles, 4 book chapters and 35 abstracts, and presented lectures at numerous conferences, served as a member on numerous editorial boards and scientific or medical advisory boards, and have a membership in numerous societies, such as American Association of Pharmaceutical Physicians, American College of Emergency Physicians, and American College of Physicians.

5. One of my main fields of research and interest is in the field of Internal Medicine, in particular primary care product, cardiovascular, and infectious diseases.

6. I have read and understand U.S. Patent Application Serial No. 10/031,556, and I am familiar with the September 29, 2003 Office Action in the above-identified application.

7. The invention disclosed in that application is directed to a method of treating sexual dysfunction (Claims 11-17 and 20-23), including, but not limited to, male erectile dysfunction and female sexual arousal disorder, which comprises orally administering to a patient in need thereof one or more unit dose containing about 1 to about 20 mg of Compound (I), up to a maximum total dose of 20 mg per day.



(I)

8. The present invention is based on detailed experiments and clinical trials, and the unexpected discovery of a unit dosage form incorporating about 1 to about 20 mg of Compound (I) that, when orally administered, effectively treats sexual dysfunction and substantially reduces various undesirable adverse events.

9. The new and surprisingly unexpected results achieved by the present invention are illustrated in Example 7 of the specification and in an analysis of pooled data from eight subsequent Phase 3 clinical trials. Example 7 shows that compound (I) is efficacious in the treatment of erectile dysfunction at 2 mg, 5 mg, and 10 mg dosages.

10. Example 7 also shows the unexpected decrease in treatment-emergent adverse events in the table at page 32 of the specification. The results in the table of Example 7 were further corroborated in controlled Phase 3 studies. The results of an analysis of pooled data from eight Phase 3 studies for placebo, 5 mg, 10 mg, and 20 mg doses are set forth in the following table, together with the data from the table of Example 7 for placebo and the 50 mg dose. The Phase 3 studies were conducted using 20 mg or lower doses because higher doses above 20 mg of Compound (I) had a sufficient number of adverse events such that the dose would have reduced tolerability to the general public.

	Placebo [1]	Tadalafil 5 mg [1]	Tadalafil 10 mg [1]	Tadalafil 20 mg [1]	Placebo [2]	Tadalafil 50 mg [2]
Adverse Event	**(N=476)**	**(N=151)**	**(N=394)**	**(N=635)**	**(N=134)**	**(N=59)**
Headache	5%	11%	11%	15%	10%	34%
Dyspepsia	1%	4%	8%	10%	6%	20%
Back pain	3%	3%	5%	6%	5%	24%
Myalgia	1%	1%	4%	3%	3%	20%
Nasal congestion	1%	2%	3%	3%	--	--
Flushing	1%	2%	3%	3%	0%	3%
Pain in limb	1%	1%	3%	3%	--	--

(1) Data from an analysis of pooled data from eight controlled Phase 3 studies (Table 7, CIALIS US Packet Insert, Nov 2003) coded using Medical Dictionary for Regulatory Activities (version 5.0); adverse events with ≥2% incidence on tadalafil (10 or 20 mg) and more frequent on drug than placebo, and

(2) Data from table of Example 7 of specification (an analysis of data pooled from three Phase 2 studies (LVBF/DSD06, LVBG/DSD04 and LVAC); adverse events coded using the COSTART dictionary).

11. The data in paragraph 10 shows a dramatic reduction in adverse events associated with common adverse events, such as headache, dyspepsia and back pain between the 20 mg and 50 mg dosages, and further reductions for the 5 mg and 10 mg dosages. This decrease of adverse events coupled with an efficacy across the claimed dose range is an unexpected advance in the art.

12. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or document or any patent resulting therefrom.

Gregory D. Sides M.D.
Gregory D. Sides, M.D.

Date: 13 Jan, 2004

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

WILLIAM E. PULLMAN ET AL.

Serial No.: 10/031,556

Filed: October 19, 2001

For: **UNIT DOSAGE FORM**

Attorney Docket No. 29342/36206A

Group Art Unit: 1614

Examiner: Rebecca Cook

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: January 12, 2004

James J. Napoli
Registration No. 32,361
Attorney for Applicants

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE-PATENTING REJECTION OVER AN ISSUED PATENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

The undersigned, having power of attorney from the assignee, Lilly ICOS LLC, has executed this document on behalf of petitioner, Lilly ICOS LLC. Petitioner is a Delaware limited liability company, 1209 Orange Street, Wilmington, Delaware 19801, and is the owner of 100% interest in the instant application, as shown by the assignment recorded March 25, 2002, at Reel 12740, Frame 679. Petitioner hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration

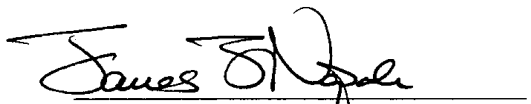
date of the full statutory term defined in 35 U.S.C. §154 to §156 and §173, as presently shortened by any terminal disclaimer of prior Patent No. 6,451,807. Petitioner also is the owner of 100% interest in U.S. Patent No. 6,451,807 as shown by the assignment recorded on August 3, 2000 at Reel 11017, Frame 503. Petitioner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and U.S. Patent No. 6,451,807 are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, petitioner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §154 to §156 and §173 of prior Patent No. 6,451,807, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. §1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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; further, these statements are made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereof.

The Commissioner is hereby authorized to credit any overpayment or charge any additional fees which may be required during the pendency of this application under 37 C.F.R. §1.16 or 37 C.F.R. §1.17 or under applicable rules (except payment of issues fees), to Deposit Account No. 13-2855. A copy of this transmittal is enclosed.



James J. Napoli
Registration No. 32,361

Dated: January 12, 2004

☒ Our firm check in the amount of $110.00 is enclosed in payment of the requisite Terminal Disclaimer fee under 37 C.F.R. §1.20(d).

411

1614

PTO/SB/22 (08-03)
Approved for use through 7/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket No. (Optional) 29342/36206A

In re Application of	William E. Pullman et al.		
Application Number	10/031,556-Conf. #6526	Filed	October 19, 2001
For:	UNIT DOSAGE FORM		
Art Unit	1614	Examiner	R. Cook

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

[x]	One month (37 CFR 1.17(a)(1))	$ 110.00
[ ]	Two months (37 CFR 1.17(a)(2))	$
[ ]	Three months (37 CFR 1.17(a)(3))	$
[ ]	Four months (37 CFR 1.17(a)(4))	$
[ ]	Five months (37 CFR 1.17(a)(5))	$

[ ] Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $ _____ .

[x] A check in the amount of the fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[ ] The Director has already been authorized to charge fees in this application to a Deposit Account.

[x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 13-2855 .
I have enclosed a duplicate copy of this sheet.

I am the
[ ] applicant/inventor.
[ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).
[ ] attorney or agent of record. Registration Number _____
[x] attorney or agent under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a) 32,361

January 12, 2004 — Date
Signature
(312) 474-6614 — Telephone Number
James J. Napoli — Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below

[ ] Total of 1 forms are submitted.

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: January 12, 2004 Signature _____ (James J. Napoli)

01/16/2004 CNGUYEN 00000070 10031556
01 FC:1251 110.00 OP

PTO/SB/17 (10-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 220.00

Complete if Known	
Application Number	10/031,556-Conf. #6526
Filing Date	October 19, 2001
First Named Inventor	William E. Pullman
Examiner Name	R. Cook
Art Unit	1614
Attorney Docket No.	29342/36206A

METHOD OF PAYMENT *(check all that apply)*

☒ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

Deposit Account Number: 13-2855

Deposit Account Name: MARSHALL, GERSTEIN & BORUN LLP

The Director is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☒ Credit any overpayments

☐ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims	Fee from below	Fee Paid
Total Claims		-20** =		x =	
Independent Claims		-3** =		x =	
Multiple Dependent				=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	110.00
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify)				Terminal Disclaimer fee	110.00

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 220.00

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Jam es J. Napoli	*Registration No. (Attorney/Agent)*	32,361	*Telephone*	(312) 474-6614
Signature	James J. Napoli			*Date*	January 12, 2004

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: January 12, 2004 Signature: James J. Napoli (James J. Napoli)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

4743 7590 05/21/2004

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
COOK, REBECCA	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 05/21/2004

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

Office Action Summary	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

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

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-17 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-17, 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

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

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Terminal Disclaimer

The terminal disclaimer filed on January 12, 2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 6,451,807 has been reviewed and is accepted.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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

Claims 11-17 and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over 6,140,329 (Daugan) for the reasons given in Paper No. 5.

The Declaration under 37 CFR 1.132 of January 15, 2004 by Dr. Sides has been thoroughly considered but is not persuasive because decreased side effects are expected at lower doses. There is no showing of similar efficacy comparing 20 mg of the compound of the instant method with the 50 mg disclosed by Daugan.

Conclusion

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

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Cook whose telephone number is (571) 272-0571. The examiner can normally be reached on Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (571) 272-0584.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Renee Jones (571) 272-0547 in Customer Service.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The official fax number is 703-872-9806

Rebecca Cook

Primary Examiner
Art Unit 1614

May 17, 2004

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	8/29/02	7/9/03	9/16/03	5/17/04	Date	Date	Date	Date	Date
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SEARCH

Class	Sub.	Date	Exmr.
514	250	8/28/02	[illegible]
updated		4/9/03	[illegible]
updated		9/16/03	[illegible]
updated		5/17/04	[illegible]

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

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

61

AF/1614
JFW

PATENT--NO FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

WILLIAM ERNEST PULLMAN ET AL.

Serial No.: 10/031,556

Filed: October 19, 2001

For: **UNIT DOSAGE FORM**

Attorney Docket No. 29342/36206A

Group Art Unit: 1614

Examiner: Rebecca Cook

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: May 20, 2004

James J. Napoli
Registration No. 32,361
Attorney for Applicants

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to their duty of disclosure under 37 C.F.R. §1.56, applicants hereby bring to the examiner's attention patent documents 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, applicants enclose a completed Form PTO-1449 listing the possibly pertinent patent documents and a copy of each document.

This Second Supplemental Information Disclosure Statement is submitted more than three months after the filing date of the above-identified applica-

tion, and after the mailing date of a first Office Action on the merits.

However, each item of information contained in this Second Supplemental Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Second Supplemental Information Disclosure Statement (37 C.F.R. §1.97(e)(1)). Accordingly, no fee as set forth in 37 C.F.R. §1.17(p) is due.

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 European Search Report is enclosed for the convenience of the examiner and to complete the file. Several references cited in the European Search Report are not cited in this Second Supplemental Information Disclosure Statement. These references were cited in previously filed Information Disclosure Statements.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

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Chicago, Illinois
May 20, 2004

Form 1449PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/031,556
Filing Date	October 19, 2001
First Named Inventor	William Ernest Pullman
Group Art Unit	1614
Examiner Name	Rebecca Cook
Attorney Docket Number	29342/36206A

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document	Publication Date MM-DD-YYYY
		WO 99 59584	11/25/1999
		WO 00 53148	09/14/2000
		WO 00 66114	11/09/2000
		WO 01 80860	11/01/2001

OTHER PRIOR ART – NONPATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published.

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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(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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Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(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

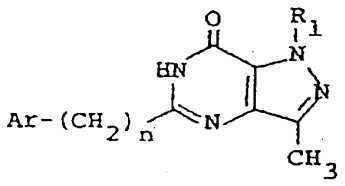
Humans include, of course, males and females. Although the pharmaceutical compositions of the present invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction. Such female sexual dysfunction 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



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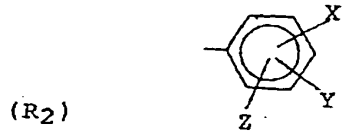
and the pharmaceutically acceptable salts thereof, in which:

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;

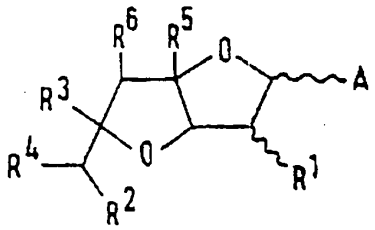
1,3-dimethyl-5-(4-sulfonic acid phenyl)pyrazolo-[4,3-d]-pyrimidine-7-one;

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.

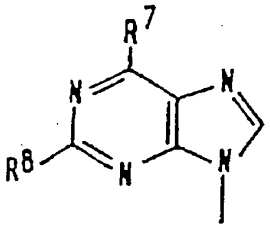
European published application number 0214708, which discloses compounds of the formula

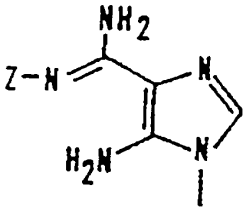


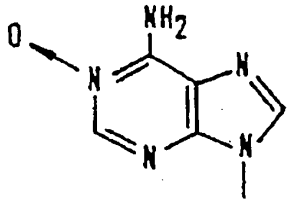
(I)

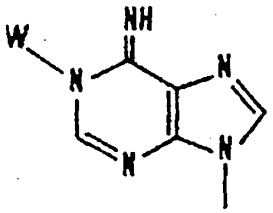
in which:

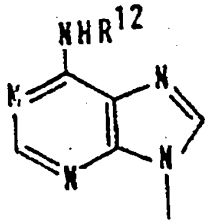
A represents a group of formula:

(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 $-OR^{11}$;

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^3 represents a hydrogen atom, a halogen atom or a group of formula $-OR^3$, $-NR^{10}R^{11}$ or $-SR^3$;

R^4 represents a halogen atom or a group of formula $-OR^3$, $-NR^{10}R^{11}$ or $-SR^3$;

R^5 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^{10} and R^{11} are the same or different and each represents a hydrogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 hydroxyalkyl group, a C_1-C_6 aminoalkyl group, an aralkyl group, an aryl group, a C_1-C_6 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_6 alkyl and/or C_1-C_6 alkoxy substituents;

R^{12} represents a C_1-C_6 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^4 and R^5 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 6'-methoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

2-Amino-N6'-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.

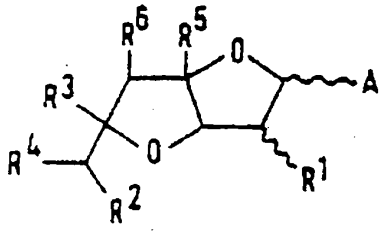
2-Acetylamino-6-desamino-6-hydroxy-4',5'-dihydro-7'-desoxygriseolic acid and pharmaceutically acceptable salts and esters thereof.

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.

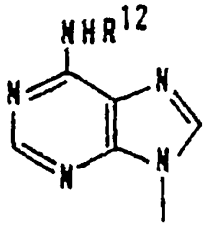
2-Chloro-4',5'-dihydrogriseolic acid and pharmaceutically acceptable salts and esters thereof.

European published application number 0319050, which discloses compounds of the formula



(I)

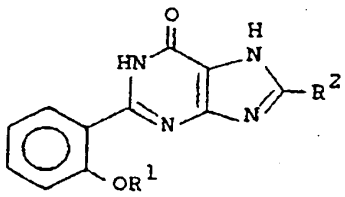
in which:
A represents a group of formula:



;

R^1 and R^2 are the same or different and each represents a hydrogen atom, a halogen atom or a group of formula $-OR^9$;
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^9 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



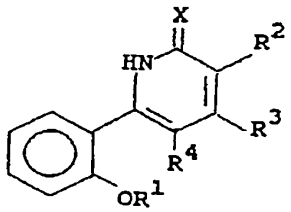
(1)

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



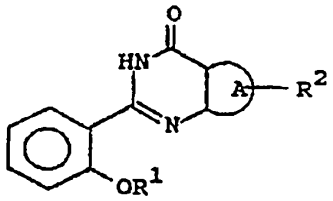
(1)

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.

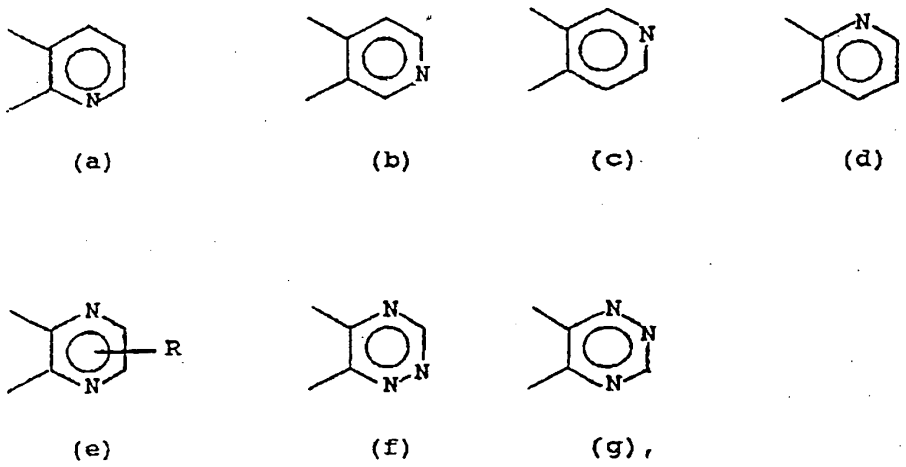
European published application number 0347146, which discloses compounds of the formula



(1)

or a pharmaceutically acceptable salt thereof, wherein

is a ring of sub-formula (a), (b), (c), (d), (e), (f) or (g) :

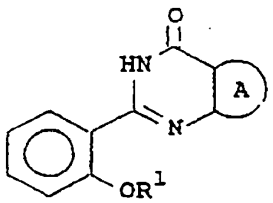


R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups;
R^2 is C_{1-5}alkylthio, C_{1-5}alkylsulphonyl, C_{1-5}alkoxy, hydroxy, hydrogen, hydrazino, C_{1-6}alkyl, phenyl, -NHCOR^3 wherein R^3 is hydrogen or C_{1-6}alkyl, or -NR^4R^5 wherein 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_{3-5}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; 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.

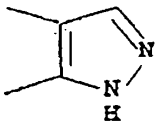
European published application number 0349239, which discloses compounds of the formula



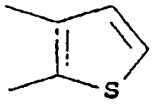
(1)

or a pharmaceutically acceptable salt thereof, wherein

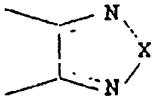
is a ring of sub-formula (a), (b) or (c):



(a)



(b)



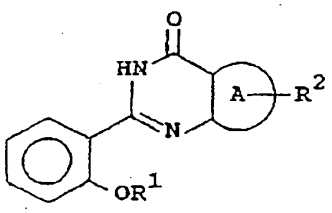
(c),

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_{1-4}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.

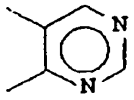
European published application number 0351058, which discloses compounds of the formula



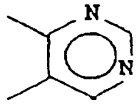
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}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$_2$R^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

is a ring of sub-formula (a) or (b) :



(a)



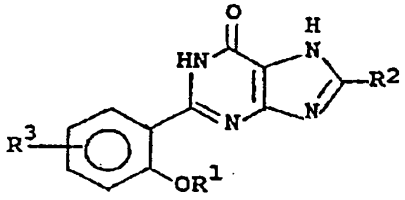
(b).

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



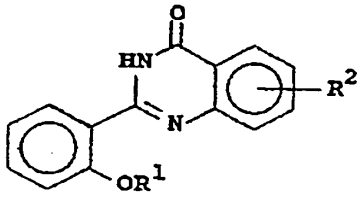
(1)

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-6,8-dione,
2-(2-benzyloxyphenyl)purin-6,8-dione,
2-(2-propoxyphenyl)-8-trifluoromethylpurin-6-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



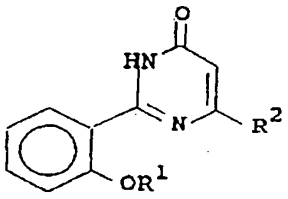
(1)

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



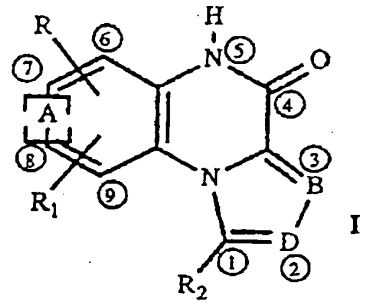
(1)

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_{1-5}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:

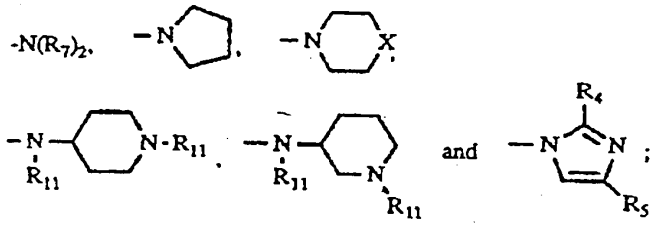
6-amino-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-acetamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-propionamido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-butyramido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
6-N'-methylureido-2-(2-propoxyphenyl)pyrimidin-4[3H]-one,
4,6-dihydroxy-2-(2-propoxyphenyl)pyrimidine,
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

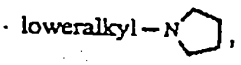


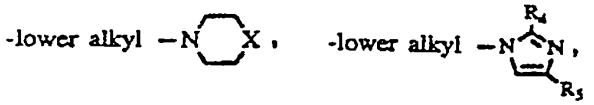
I

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-,

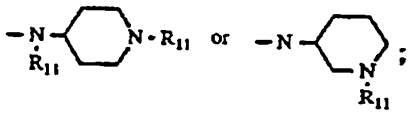


R_2 is hydrogen, lower alkyl, phenyl which may be substituted by up to three methoxy groups, lower alkyl substituted by phenyl which may be substituted by up to three methoxy groups, - lower alkyl $-N(R_8)_2$,

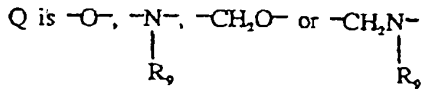


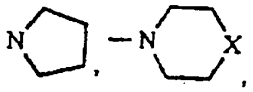


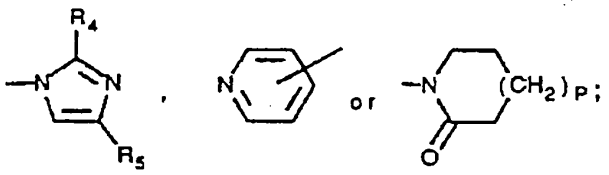
pyridinyl or lower-alkyl pyridinyl;
R_3 is hydrogen, lower alkyl, phenyl, lower alkylphenyl, pyridinyl or loweralkyl pyridinyl;
R_4, R_5 are the same or independently hydrogen or lower alkyl;
R_6 is lower alkyl, phenyl, lower alkylphenyl or pyridinyl;
R_7 are the same or independently hydrogen, loweralkyl, phenyl, pyridinyl,



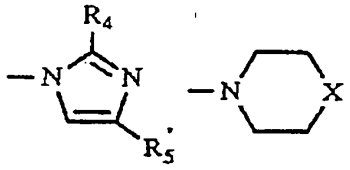
R_8 are the same or independently lower alkyl, phenyl or pyridinyl;

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

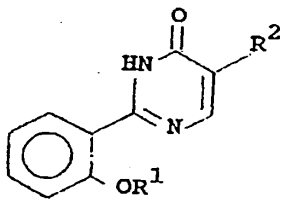


or W-ALK-Q-;
and the pharmaceutically acceptable salts thereof.

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



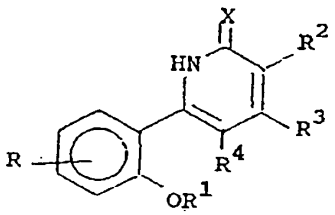
(1)

or a pharmaceutically acceptable salt thereof, wherein
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkylC_{1-6}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;

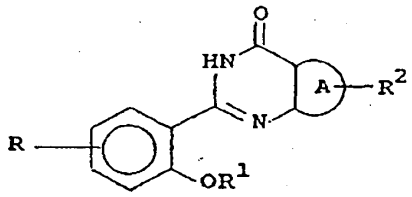
R^2 is hydrogen, -CN, $-CONR^5R^6$, $-CO_2R^7$,5-tetrazolyl, $-NO_2$, $-NH_2$ or $-NHCOR^8$ wherein R^5 to R^8 are independently hydrogen or C_{1-4}alkyl;
R^3 is hydrogen or C_{1-4}alkyl;
R^4 is hydrogen or C_{1-4}alkyl; and
R is halo, C_{1-4}alkyl, C_{1-4}alkoxy, cyano, $-CONR^9R^{10}$, $-CO_2R^{11}$, $-S(0)_nC_{1-4}$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-propoxyphonyl)-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.

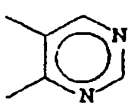
European published application number 0442204, which discloses compounds of the formula



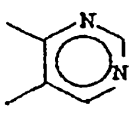
(1)

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^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

A is a ring of sub-formula (a) or (b) :

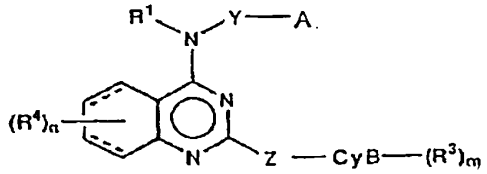


(a)



(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-$(R^2)_1$,
(ii) -O-R^0 or -S(O)$_p$-R^0, or
(iii) -$NR^{16}R^{17}$;
in which R^0 is hydrogen, C_{1-4} alkyl, hydroxy-C_{1-4} alkyl or -CyA-$(R^2)_1$;
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) -$COOR^6$, in which R^6 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-$(R^2)_1$ 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^0 or -S(O)$_p$-R^0 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,
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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,
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4-phenylmethylamino-6-trifluoromethoxy-2-(1-imidazolyl)quinazoline,
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4-phenylmethylamino-6-cyano-2-(1-imidazolyl)quinazoline,
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4-phenylmethylamino-2-((1-imidazolyl)methyl)quinazoline,
4-phenylmethylamino-2-(2-methyl-1 -imidazolyl)quinazoline,
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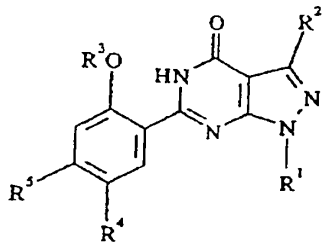
6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline,
6-chloro-4-(3-carboxyphenyl)amino-2-(1 -imidazolylmethyl)quinazoline,
6-dimethylaminosulfonyl-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
6,7-dimethoxy-4-phenylmethylamino-2-(1-imidazolyl)quinazoline,
4-(3,4-dimethoxyphenylmethyl)amino-2-(1-imidazolyl)quinazoline,
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)

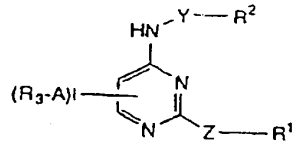
and salts and solvates (e.g. hydrates) thereof, in which:
R^1 represents arylmethyl or C_{1-6}alkyl optionally substituted by one or more fluorine atoms;
R^2 represents methyl;
R^3 represents C_{2-4}alkyl;
R^4 represents nitro, cyano, C_{1-6}alkoxy, $C(=X)NR^6R^7$, NR^8R^9, $(CH_2)_mNR^{10}C(=Y)R^{11}$ 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}alkyl-piperazine 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



(I)

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 carbocydic ring,
(iii) C1-4 alkoxy,
(iv) hydroxy(C1-4 alkoxy) or
(v) hydroxy;

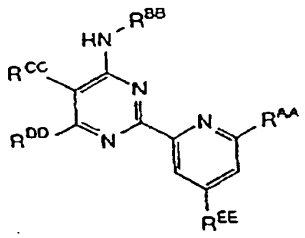
R3 is (i) 4-15 membered heterocydic ring containing one or two hetero atoms chosen from nitrogen, oxygen and sulphur, not more than one hetero atom being oxgen or sulphur, optionally substituted by one or two groups chosen from C1-4 alkyl, C1-4 alkoxy, halogen, trifluoromethyl, nitro, cyano, ethynyl and groups of formula:

-SONR7R8

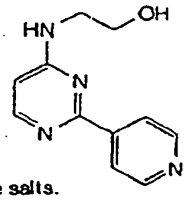
wherein R7 and R8 are independently hydrogen or C1-4 alkyl.
(ii) C4-15 carbocydic ring,
(iii) a group of formula:

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:



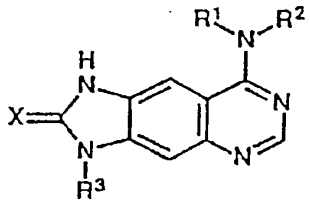
and its pharmaceutically acceptable salts.

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

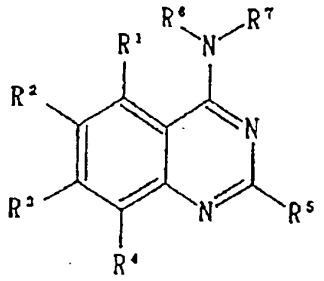
European published application number 0668280, which discloses compounds of the formula



(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



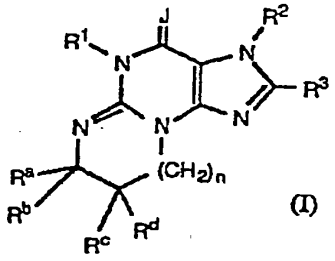
(I)

(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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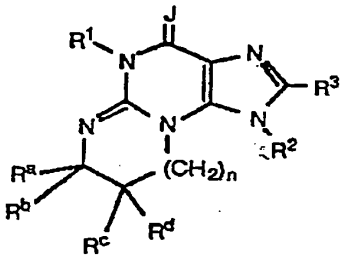
and



(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)-

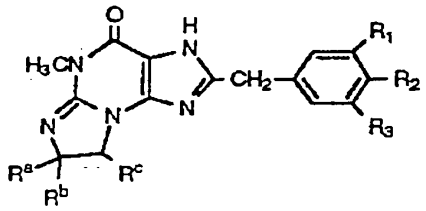
cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
cis-5,6a,7,8,9,9a-Hexahydro-5-methyl-3-(2-naphthylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3*H*)-one;
bromophenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
5,6a(R)-7,8,9,9a(S)-Hexahydro-2,5-dimethyl-3-(4-methoxyphenylmethyl)-cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one;
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-methyl-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;

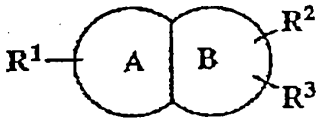
(+)-2-benzyl-7, 8-dihydro-5-methyl-7-(1-methylethyl)-1H-imidazo[2,1-b]-purin-4(5H)-one;

(+,-)-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;

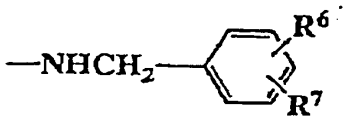
R^1 represents a group represented by the formula: $-NR^4R^5$ (wherein R^4 and R^5 may be the same or different

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:

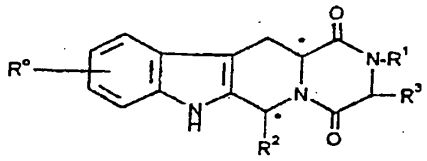
(wherein R^8 represents a carboxyl or tetrazolyl group which may be protected),
or a halogen atom;
and

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

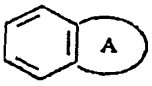


(I)

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

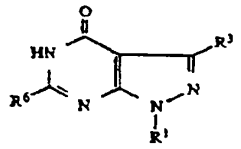
R^3 represents hydrogen or C_{1-3} alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain.

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:

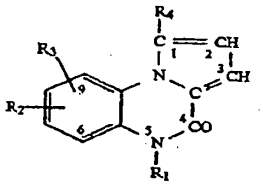
R^1 is hydrogen, alkyl, C_4 to C_7 cycloalkyl, C_4 to C_7 cycloalkyl substituted by C_1 to C_{10} alkyl or hydroxyl, 2- or 3-tetrahydrofuranyl, 3-tetrahydrothienyl 1,1, -dioxide, C_4 to C_7 cycloalkyl-C_1 to C_{10} alkyl, carboxy-C_1 to C_{10} alkyl, carbo-C_1 to C_4 lower-alkoxy-C_1 to C_{10} alkyl, 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

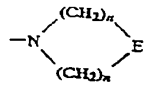
where Alk: is C_1–C_6-alkyl, C_2–C_6-hydroxyalkyl or C_3–C_6-cycloalkyl and the symbol A represents:

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

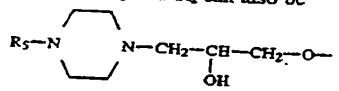
where D is phenyl, C_1–C_6-alkyl, C_3–C_7-cycloalkyl, hydroxy, C_1–C_6-alkoxy, C_3–C_7-cycloalkyloxy, morpholino, pyrrolidino, piperidino, homopiperidino, piperazino, —NHR_5 or —NR_5R_6 and R_5 and R_6 have the meanings given hereinabove;

4) The group:

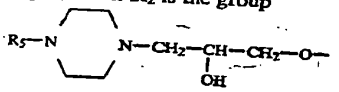


where n can be the integers 1-3 and E represents CH_2, oxygen, sulfur, NH, CHOH, CH—C_1-C_6-alkyloxy, CH—C_2-C_6-alkanoyloxy, CHC_6H_5, CHCOD, CH—$CH_2C_6H_5$, N—C_1-C_6-alkyl, N—C_1-C_6-hydroxyalkyl, N—C_6H_5, N—$CH_2C_6H_5$, N—$CH(C_6H_5)_2$, N—$(CH_2)_2$—OH, N—$(CH_2)_3$—OH or NCOD and the phenyl 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

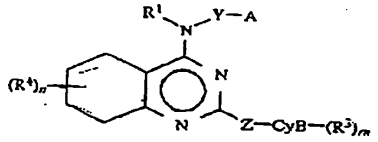


R_4: hydrogen or halogen, where R_1 can also be hydrogen, when R_2 is the group



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,

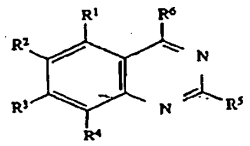
and pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

4-(2-methylthioethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,

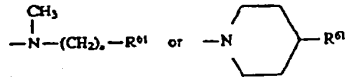
4-(2-methylsulfinylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(2-methylsulfonylethyl)amino-6-methoxy-2-(1-imidazolyl)quinazoline,
4-(3-trifluoromethylphenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-(N,N-dimethylamino)phenylmethyl)amino-2-(3-pyridyl)quinazoline,
4-(4-sulfamoylphenylmethyl)amino-2-(3-pyridyl)-quinazoline,
4-(4-trifuloromethoxyphenylmethyl)amino-2-(1-imidazolyl)qninazoline,
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

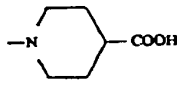
U.S. Patent No. 5,576,322 discloses compounds of the formula


(I)

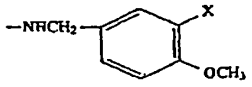
wherein R1, R3, and R4, each of which may be the same or different from each other, may each represent a hydrogen atom, a halogen atom or a lower alkyl group or a lower alkoxy hydrogen atom, R2 is a halogen or cyan group R5 is a group represented by the formula:



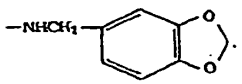
wherein u is 3 or 4 and R61 represents a carboxyl group which may be protected or a heternaryl group; or R5 is a group represented by the formula:



and R6 is a group represented by the formula



wherein X is hydrogen atom or a halogen atom or



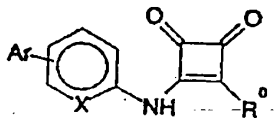
or the pharmacologically acceptable salt thereof.

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)anilino]-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,

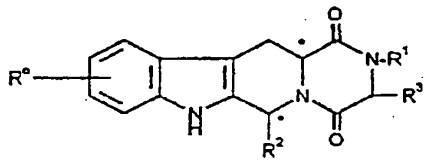
3-amino-4-[3-(2-imidazolyl)anilino]-3-cyclobutene-1,2-dione,

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

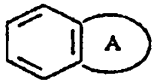


(I)

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;

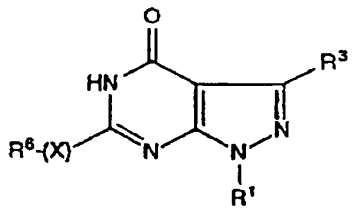
R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring  attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which 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:

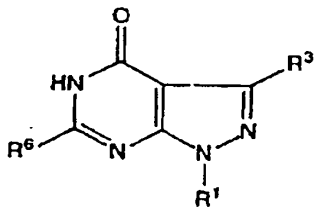
1-cyclopentyl-3-ethyl-6-(4-methoxyphenylmethyl)pyrazolo [3,4-d]pyrimindin-4-one,

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,

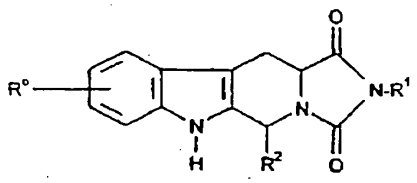
1-cyclopentyl-3-ethyl-6-[4-(1-imidazolyl)phenyl]pyrazolo [3,4-d]pyrimindin-4-one,

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

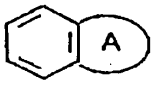
(e) a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from oxygen, nitrogen and sulphur, and being optionally substituted by one or more C_{1-6}alkyl, and optionally linked to the nitrogen atom to which R^1 is attached via C_{1-6}alkyl;

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:

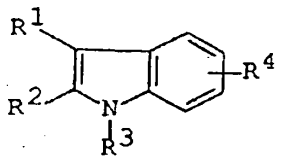
Cis-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Trans-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo [1',5':1,6]pyrido[3,4-b]indole-1,3(2H)-dione;
Cis-5-(4-methoxyphenyl)-2-methyl-5,6,11,11a-tetrahydro-1H-imidazo [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

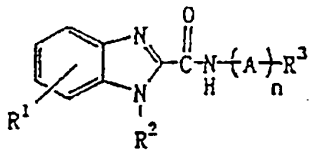
optionally substituted with protected carboxy, carboxy or acyl;

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 pyridylcarbonyl 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.

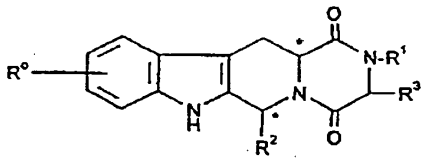
1-Benzyl-6-chloro-2-{1-[3-(1,2,4-triazol-1-yl)propyl]indol-5-ylaminocarbonyl}benzimidazole.

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

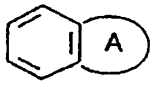


(I)

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 or alkenyl chain;

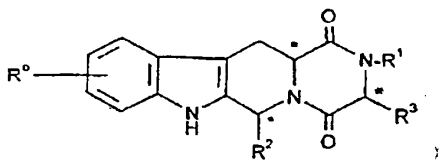
for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

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



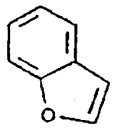
(I)

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

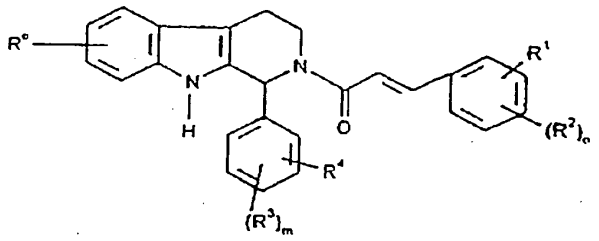
R^3 represents hydrogen or C_{1-3}alkyl.

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 - $C(=O)OR^a$ or C_{1-4}alkyl),

-C_{1-6}alkyl optionally substituted by -OR^a,

-C_{1-3}alkoxy,

-$C(=O)R^a$,

-O-$C(=O)R^a$,

-$C(=O)OR^a$,

-C_{1-4}alkylene $C(=O)OR^a$,

-O-C_{1-4}alkylene -$C(=O)OR^a$,

-C_{1-4}alkylene-O-C_{1-4}alkylene-$C(=O)OR^a$,

-$C(=O)NR^aSO_2R^c$,

-$C(=O)C_{1-4}$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^aR^b,

-$C(=O)NR^aR^b$,

-$C(=O)NR^aR^c$,

-$C(=O)NR^aC_{1-4}$alkylene OR^b

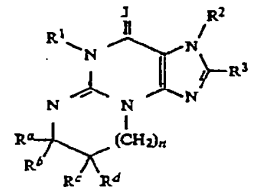
-$C(=O)NR^aC_{1-4}$alkylene Het, wherein Het represents a 5- or 6-membered

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(=O)-OR^b,
-NR^aR^b,
-NR^aC_{1-4}alkyleneNR^aR^b,
-$NR^aC(=O)R^b$,
-$NR^aC(=O)NR^aR^b$,
-$N(SO_2C_{1-4}alkyl)_2$,
-$NR^a(SO_2C_{1-4}alkyl)$,
-$SO_2NR^aR^b$, 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
-$C(=O)OR^a$;
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 -$C(=O)OR^a$ or one or more -OR^a;

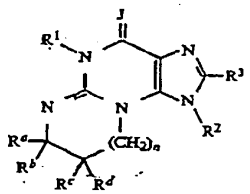
n is an integer selected from 1, 2 and 3;
m is an integer selected from 1 and 2;
and pharmaceutically acceptable salts and solvates thereof.

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 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)-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-

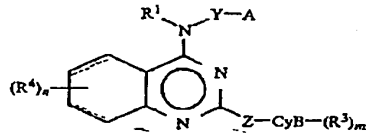
carboxylic acid, methyl ester;
cis-5,6a,7,8,9,9a-Hexahydro-2-bromo-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one;
cis-5,6a,7,8,9,9a-Hexahydro-2-(methylaminosulfonyl)-5-methyl-3-(phenylmethyl)cyclopent[4,-5]imidazo[2,1-b]purin-4(3H)one;
cis-1-Cyclopentyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-b]purin-4-(1H)one;

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)-onc;
(+/−) 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); 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



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;

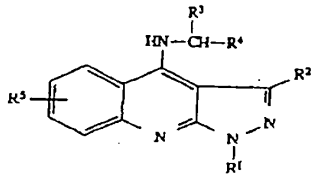
or pharmaceutically acceptable acid addition salts thereof, pharmaceutically acceptable salts thereof, or hydrates thereof.

Preferred compounds include:

4-[2-(2-hydroxycthoxy)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,

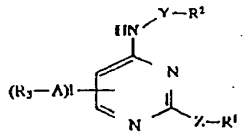
1-ethyl -6-nitro-N-[cyclohexylmethyl]- 1H-pyrazolo [3,4-b]quinolin-4-amine,

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,

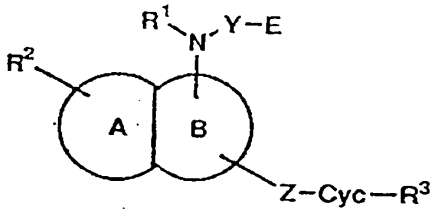
or pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable salts thereof.

Preferred compounds include

2-(1-Imidazolyl)-4-[2-(2-hydroxyethoxy)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)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,

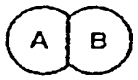
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-methoxyphenyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-furyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-thienyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(3-pyridyl)methylaminopyrimidine,
2-(1-Imidazolyl)-5-(2-thienyl)-4-(2-methoxyethyl)aminopyrimidine,
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

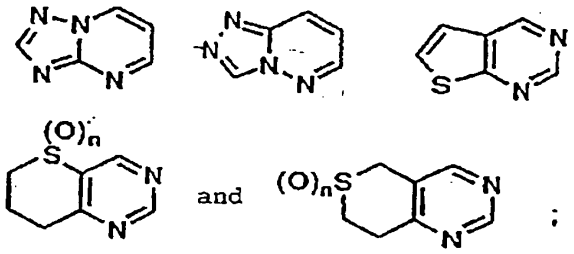


(I)

wherein



is a heterocycle selected from



;

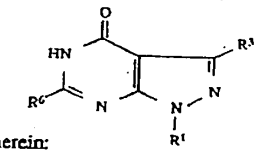
n is 0, 1 or 2;
Y is single bond or C1-6 alkylene;
Z is single bond, C1-2 alkylene or vinylene;
E is

(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,

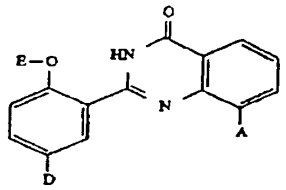
1-Cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)pyrazolo[3,4-d]pyrimidin-4-one,

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,

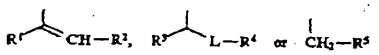
U.S. Patent No. 5,721,238 discloses compounds of the formula



(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,

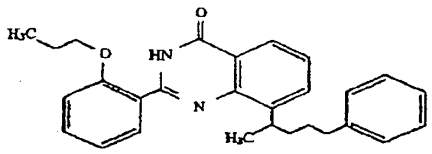
D represents hydrogen, or represents a group of the formula $—SO_2—NR^8R^9$,

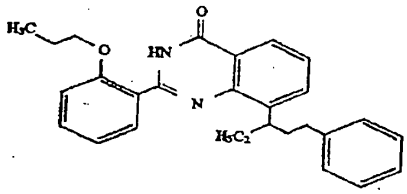
wherein

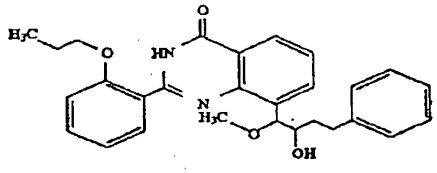
R^8 and R^9 are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, or, together with the nitrogen atom, form a 5- to 6-membered saturated heterocyclic radical which has up to 2 further hetero 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

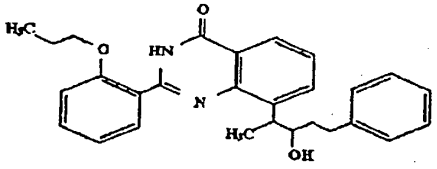
E represents straight-chain or branched alkyl having up to 8 carbon atoms, and tautomers and salts thereof.

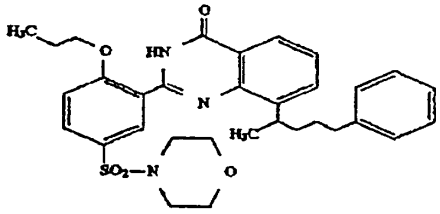
Preferred compounds include:

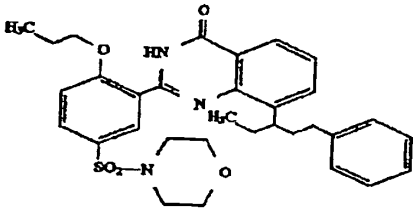




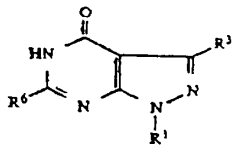








U.S. Patent No. 5,294,612 discloses compounds of the formula



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;

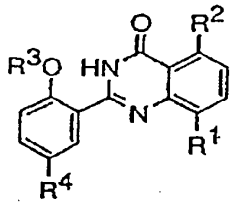
R^3 is, C_1 to C_4 lower-alkyl, phenyl-C_1 to C_4 lower-alkyl, lower-alkoxyphenyl-C_1 to C_4 lower-alkyl, diC_1 to C_4 lower-alkoxy-phenyl-C_1 to C_4 lower-alkyl, pyridyl-C_1 to C_4 lower-alkyl, C_4 to C_7 cycloalkyl-C_1 to C_4 lower-alkyl, phenylamino, diC_1 to C_{10} alkylamino, halogen, trifluoromethyl, 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;

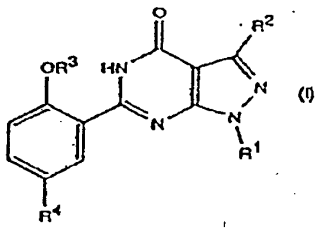
8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one;

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_4 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;

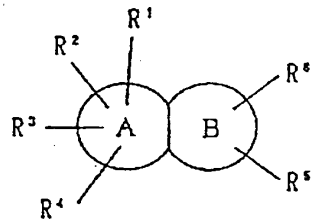
6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

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

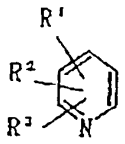


(1)

[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.

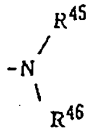
Provided that the ring A and the ring B are combined sharing two atoms and the atoms shared may be either a carbon atom or a nitrogen atom.

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

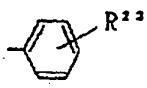
(wherein R^7 represents a lower alkyl group, and n represents 0 or an integer of 1 to 2), or a group represented by the formula



(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

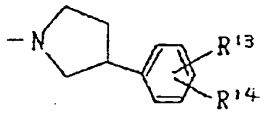
(wherein R^8 represents a lower alkyl group, and m represents 0 or an integer of 1 to 2), a group represented by the formula $-O-R^9$ (wherein R^9 represents a hydroxyalkyl group which may be protected, a carboxyalkyl group which may be protected or a benzyl group which may be substituted), a group represented by the formula



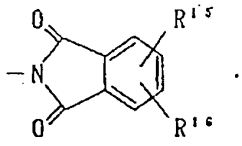
(wherein R^{23} represents a hydroxyl group, a lower alkyl group, a lower alkoxy group, a hydroxyalkyl group or a hydroxyalkyloxy group), a heteroaryl group which may be substituted, a 1,3-benzdioxolyl group which may be substituted, a 1,4-benzdioxyl group which may be substituted, a 1,3-benzdioxolylalkyl 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).

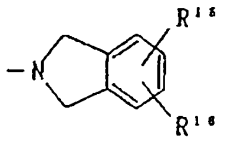
R^6 represents a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a lower alkyl group, a lower alkoxy group, a lower alkenyl group, a 1,3-benzdioxolylalkyloxy group, a 1,4-benzdioxylalkyloxy group, a phenylalkyloxy group which may be substituted, a group represented by the formula



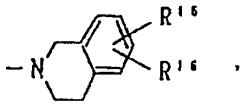
(wherein R^{13} and R^{14}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{13} and R^{14} may together form methylenedioxy or ethylenedioxy), a group represented by the formula



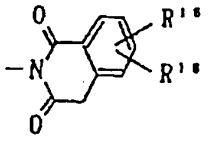
a group represented by the formula



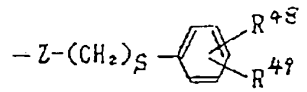
a group represented by the formula



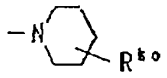
a group represented by the formula



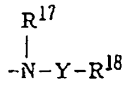
(in these formulas, R^{15} and R^{16}, each of which may be the same or different from each other, represent each a hydrogen atom, a lower alkyl group or a lower alkoxy group; or, further, R^{15} and R^{16} may together form methylenedioxy or ethylenedioxy), a piperidine-4-spiro-2'-dioxan-1-yl group, 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

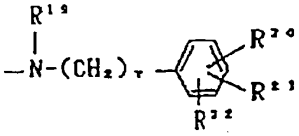


(wherein R^{50} represents a hydroxyl group, a halogen atom, a lower alkyl group, a lower alkoxy group, a carboxyl group which may be protected, a cyano group, a hydroxyalkyl group or a carboxyalkyl group), a group represented by the formula



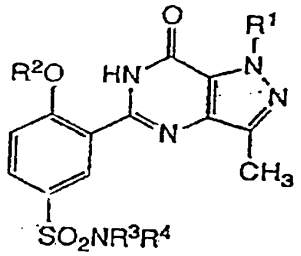
[wherein R^{17} represents a hydrogen atom, a lower alkyl group, an acyl group, a lower alkoxyalkyl group, a carboxyalkyl group which may be protected or a hydroxyalkyl group; Y represents a group represented by the formula $-(CH_2)_q-$ (wherein q is 0 or an integer of 1 to 8), or a group represented 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;

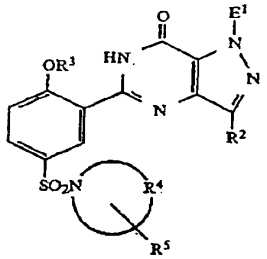
1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

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;

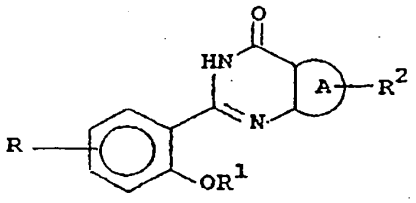
R^3 is C_1–C_6 alkyl, C_3–C_6 alkenyl, C_3–C_6 alkynyl, C_3–C_7 cycloalkyl, C_1–C_6 perfluoroalkyl or (C_3–C_6 cycloalkyl)C_1–C_6 alkyl;

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

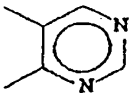
R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-5}cycloalkyl C_{1-6}alkyl, or C_{1-6}alkyl substituted by 1 to 6 fluoro groups ;

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

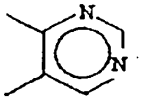
n is 0, 1 or 2, -OR^6, -CO_2R^7 or -NR^8R^9 wherein R^6 to R^9 are independently hydrogen or C_{1-6}alkyl, provided that the carbon atom adjacent to the nitrogen atom is not substituted by said -$S(O)_nC_{1-6}$alkyl, -OR^6 or -NR^8R^9 groups ;

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)

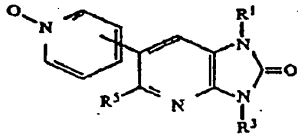


(b).

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

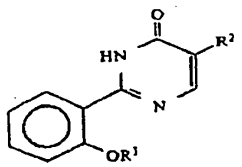


wherein
R_1 and R_3 are hydrogen or lower-alkyl;
R_5 is lower-alkyl or fluorinated lower-alkyl; and the pyridine-N-oxide is attached at the 4- or 3-position; or a pharmaceutically acceptable acid-addition salt thereof.

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



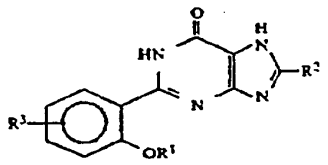
(I)

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



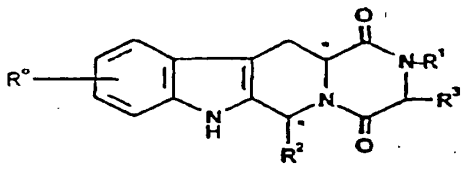
(I)

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:

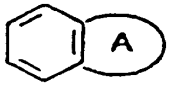


(I)

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

R^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.

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 treating 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

Inter onal 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

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PC1/US 99/07046

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(54) Title: METHODS AND COMPOSITIONS FOR TREATING ERECTILE DYSFUNCTION

(57) Abstract

The present invention provides for a method for the treatment of erectile dysfunction in a male or female human subject in need of such treatment comprising administration of a therapeutically effective amount of an agonist of the melanocortin receptor in combination with a therapeutically effective amount of a cyclic–GMP–specific phosphodiesterase inhibitor or an alpha–adrenergic receptor antagonist. Further, the present invention provides for pharmaceutical compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful for treating erectile dysfunction.

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TITLE OF THE INVENTION
METHODS AND COMPOSITIONS FOR TREATING ERECTILE DYSFUNCTION

FIELD OF THE INVENTION

The present invention provides for novel methods for the treatment of erectile dysfunction comprising a drug combination. More particularly, the drug combination of the present invention comprises an agonist of the melanocortin receptor with a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. The present invention also provides for pharmaceutical compositions comprising such drug combinations useful in the methods to treat erectile dysfunction. Moreover, the present invention provides for a method of manufacture of a medicament useful in the treatment of erectile dysfunction.

BACKGROUND OF THE INVENTION

Erectile dysfunction denotes the medical condition of inability to achieve penile erection sufficient for successful sexual intercourse. The term "impotence" is oftentimes employed to describe this prevalent condition. Approximately 140 million men worldwide, and, according to a National Institutes of Health study, about 30 million American men suffer from impotency or erectile dysfunction. It has been estimated that the latter number could rise to 47 million men by the year 2000. Erectile dysfunction can arise from either organic or psychogenic causes, with about 20% of such cases being purely psychogenic in origin. Erectile dysfunction increases from 40% at age 40, to 67% at age 75, with over 75% occurring in men over the age of 50. In spite of the frequent occurrence of this condition, only a small number of patients have received treatment because existing treatment alternatives, such as injection therapies, penile prosthesis implantation, and vacuum pumps, have been uniformly disagreeable [for a discussion, see "ABC of sexual health - erectile dysfunction," Brit. Med. J. 318: 387-390 (1999)]. Only more recently have more viable treatment modalities become available, in particular orally active agents, such as sildenafil citrate, marketed by Pfizer under the brand name of Viagra®. Sildenafil is a selective inhibitor of type V phosphodiesterase (PDE-V), a cyclic-GMP-specific phosphodiesterase isozyme [see R.B. Moreland et al., "Sildenafil: A Novel Inhibitor of Phosphodiesterase Type 5 in Human Corpus Cavernosum Smooth Muscle Cells," Life Sci., 62: 309-318 (1998)]. Prior to the introduction of Viagra®

on the market, less than 10% of patients suffering from erectile dysfunction received treatment. Sildenafil is also being evaluated in the clinic for the treatment of female sexual dysfunction.

The regulatory approval of Viagra® for the oral treatment of erectile dysfunction has invigorated efforts to discover even more effective methods to treat erectile dysfunction. Several additional selective PDE-V inhibitors are in clinical trials. UK-114542 is a sildenafil backup from Pfizer with supposedly improved properties. IC-351 (ICOS Corp.) is claimed to have greater selectivity for PDE-V over PDE-VI than sildenafil. Other PDE-V inhibitors include M-54033 and M-54018 from Mochida Pharmaceutical Co. and E-4010 from Eisai Co., Ltd.

Other pharmacological approaches to the treatment of erectile dysfunction have been described [see, e.g., "Latest Findings on the Diagnosis and Treatment of Erectile Dysfunction," Drug News & Perspectives, 9: 572-575 (1996); "Oral Pharmacotherapy in Erectile Dysfunction," Current Opinion in Urology, 7: 349-353 (1997)]. A product under clinical development by Zonagen is an oral formulation of the alpha-adrenoceptor antagonist phentolamine mesylate under the brand name of Vasomax®. Vasomax® is also being evaluated for the treatment of female sexual dysfunction.

Drugs to treat erectile dysfunction act either peripherally or centrally. They are also classified according to whether they "initiate" a sexual response or "facilitate" a sexual response to prior stimulation [for a discussion, see "A Therapeutic Taxonomy of Treatments for Erectile Dysfunction: An Evolutionary Imperative," Int. J. Impotence Res., 9: 115-121 (1997)]. While sildenafil and phentolamine act peripherally and are considered to be "enhancers" or "facilitators" of the sexual response to erotic stimulation, sildenafil appears to be efficacious in both mild organic and psychogenic erectile dysfunction. Sildenafil has an onset of action of 30-60 minutes after an oral dose with the effect lasting about 4 hours, whereas phentolamine requires 5-30 minutes for onset with a duration of 2 hours. Although sildenafil is effective in a majority of patients, it takes a relatively long time for the compound to show the desired effects. The faster-acting phentolamine appears to be less effective and to have a shorter duration of action than sildenafil. Oral sildenafil is effective in about 70% of men who take it, whereas an adequate response with phentolamine is observed in only 35-40% of patients. Both compounds require erotic stimulation for efficacy. Since sildenafil indirectly increases blood flow in the systemic circulation by enhancing the smooth muscle relaxation effects of nitric

oxide, it is contraindicated for patients with unstable heart conditions or cardiovascular disease, in particular patients taking nitrates, such as nitroglycerin, to treat angina. Other adverse effects associated with the clinical use of sildenafil include headache, flushing, dyspepsia, and "abnormal vision," the latter the result of inhibition of the type VI phosphodiesterase isozyme (PDE-VI), a cyclic-GMP-specific phosphodiesterase that is concentrated in the retina. "Abnormal vision" is defined as a mild and transient "bluish" tinge to vision, but also an increased sensitivity to light or blurred vision. Moreover, since some patients have developed a tolerance to prior phosphodiesterase inhibitors, sildenafil may prove to have a similar outcome in some percentage of patients when used over a long period of time.

Synthetic melanocortin receptor agonists (melanotropic peptides) have been found to initiate erections in men with psychogenic erectile dysfunction [See H. Wessells et al., "Synthetic Melanotropic Peptide Initiates Erections in Men With Psychogenic Erectile Dysfunction: Double-Blind, Placebo Controlled Crossover Study," J. Urol., 160: 389-393 (1998); Fifteenth American Peptide Symposium, June 14-19, 1997 (Nashville TN)]. Activation of melanocortin receptors of the brain appears to cause normal stimulation of sexual arousal. In the above study, the centrally acting α-melanocyte-stimulating hormone analog, melanotan-II (MT-II), exhibited a 75% response rate, similar to results obtained with apomorphine, when injected intramuscularly or subcutaneously to males with psychogenic erectile dysfunction. MT-II is a synthetic cyclic heptapeptide, Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-NH_2, which contains the 4-10 melanocortin receptor binding region common to α-MSH and adrenocorticotropin, but with a lactam bridge. MT-II (also referred to as PT-14) (Erectide®) is presently in clinical development by Palatin Technologies, Inc. and TheraTech, Inc. as a non-penile subcutaneous injection formulation. An oral transmucosal delivery system for the drug is also being developed. It is considered to be an "initiator" of the sexual response. The time to onset of erection with this drug is relatively short (10-20 minutes) with a duration of action approximately 2.5 hours. Adverse reactions observed with MT-II include nausea, flushing, loss of appetite, stretching, and yawning.

Adverse effects associated with MT-II may be the result of the lack of selectivity of the compound for a particular melanocortin receptor subtype. To date, five melanocortin receptor subtypes have been cloned. Evidence has been presented suggesting that the erectogenic properties of melanocortin agonists are mediated *via* binding to the MC-4R subtype. Whereas MC-3R is expressed in the brain, gut, and

placenta, the MC-4R subtype is uniquely expressed in the brain, and inactivation has been found to cause obesity.

Because of the unresolved deficiencies of the various pharmacological agents discussed above, there is a continuing need in the medical arts for improved methods and compositions to treat individuals suffering from psychogenic and/or organic erectile dysfunction. Such methods should have wider applicability, enhanced convenience and ease of compliance, short onset of action, reasonably long duration of action, and minimal side effects with few contraindications, as compared to agents now available.

It is therefore an object of the present invention to provide methods of treating erectile dysfunction which comprise the administration to a human subject in need thereof a centrally-acting agent that "initiates" an erectogenic response in combination with another centrally-acting agent or a peripherally-acting agent that "facilitates" or "enhances" the response to erotic stimulation. The human subject may be either male or female.

It is another object of the present invention to provide pharmaceutical compositions comprising the combination that are useful in the methods of the present invention.

It is still a further object of the present invention to provide a method of manufacture of a medicament useful in the treatment of erectile dysfunction.

SUMMARY OF THE INVENTION

The present invention provides for methods of treating erectile dysfunction in a human subject in need of such treatment comprising administration of a therapeutically effective amount of an agonist of the melanocortin receptor in combination with a therapeutically effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. Further, the present invention provides for pharmaceutical compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful to treat erectile dysfunction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is concerned with the combination of an agonist of the melanocortin receptor with a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist for the treatment of erectile dysfunction in

a male or female human subject. This particular combination produces unexpectedly superior pharmacokinetic and pharmacodynamic results in the treatment of male or female erectile dysfunction. Thus, it is an object of the instant invention to describe the combination of the two drugs in the treatment of erectile dysfunction. In addition, it is an object of the instant invention to describe preferred embodiments within each category of compounds which are used as elements in the instant combination. It is a further object of this invention to describe compositions containing each of the compounds for use in the treatment of erectile dysfunction. It is a still further object of this invention to describe a method of manufacture of a medicament containing the present drug combination which is useful for the treatment of erectile dysfunction. Further objects will become apparent from a reading of the following description.

The instant combination for the treatment of erectile dysfunction contains as a first element an agonist of the melanocortin receptor. Representative agonists of the melanocortin receptor are disclosed in the following publications, which are incorporated by reference herein in their entirety:

(1) M. E. Hadley et al., "Discovery and Development of Novel Melanogenic Drugs," in Integration of Pharmaceutical Discovery and Development: Case Studies, edited by Borchardt et al., Plenum Press, New York, 1998;

(2) R.T. Dorr, et al., "Evaluation of Melanotan-II, A Superpotent Cyclic Melanotropic Peptide in a Pilot Phase-I Clinical Study," Life Sci., 58: 1777-1784 (1996); and

(3) R.A.H. Adan, "Identification of Antagonists for Melanocortin MC3, MC4, and MC5 Receptors," European J. Pharmacol., 269: 331-337 (1994).

Compositions and methods for the treatment of psychogenic erectile dysfunction comprising melanotropic peptides are disclosed in U.S. Patent No. 5,576,290 and CA 2,158,425, which are incorporated by reference herein in their entirety.

In the instant combination for the treatment of erectile dysfunction, the first element of the combination is an agonist of the melanocortin receptor. In one embodiment of the combination of the present invention, the agonist of the melanocortin receptor is melanotan-II (MT-II).

In another embodiment of the combination of the present invention, the agonist of the melanocortin receptor is selective for the MC-4R subtype. Selective MC-4R agonists have been described, and reference is made to the following disclosures, which are incorporated by reference herein in their entirety:

(1) C. Haskell-Luevano, et al., "Discovery of Prototype Peptidomimetic Agonists at the Human Melanocortin Receptors MC1R and MC4R," J.Med. Chem., 40: 2133-2139 (1997); and

(2) H.B. Schioth, et al., "Discovery of Novel Melanocortin-4 Receptor Selective MSH Analogues," Brit. J. Pharmacol., 124: 75-82 (1998).

In the instant combination for the treatment of erectile dysfunction, the second element of the combination is composed of either a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. In a further embodiment of the combination of the present invention, the second element of the combination is a cyclic-GMP-specific phosphodiesterase inhibitor selective for the type V phosphodiesterase isozyme (PDE-V). Representative PDE-V inhibitors are disclosed in the patent and scientific literature. The Pfizer pyrazolo[4,3-d]pyrimidin-7-one PDE-V inhibitors are disclosed in WO 94/28902; WO 96/16644; WO 96/16657; EP 0,702,555; EP 0,463,756; CA 2,163,446; and U.S. Patent No. 5,250,534; all of which are incorporated by reference herein in their entirety. Sildenafil is the generic name for 1-[4-ethoxy-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulfonyl]-4-methyl-piperazine. For a discussion of its efficacy in the treatment of male erectile dysfunction, reference is made to I. Goldstein et al., N. Engl. J. Med., 338: 1397-1404 (1998) and M. Boolell et al., "Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction," Int. J. Impotence Res., 8: 47-52 (1996).

The ICOS Corp. tetracyclic PDE-V inhibitors are disclosed in WO 95/19978; WO 97/03675; and WO 97/19978; all of which are incorporated by reference herein in their entirety. IC-351 represents (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 is disclosed in WO 97/03675 for the treatment of impotence.

The Mochida Pharmaceutical Co. pyridocarbazole series of PDE-V inhibitors, of which M-54018 and M-54033 are members, is disclosed in WO 97/45427, which is incorporated by reference herein in its entirety. Other structural classes of PDE-V inhibitors are disclosed in WO 98/16224 (E. Merck GmbH), WO 99/02161 (Forssmann), WO 98/07430 (Eisai), and JP 8225541 (Eisai), all of which are incorporated by reference herein in their entirety.

In a class of this embodiment of the present invention, the combination for the treatment of erectile dysfunction comprises an agonist of the melanocortin

receptor and a PDE-V inhibitor selected from the group consisting of sildenafil citrate, IC-351, M-54018, and M-54033. In a subclass of this class of the present invention, the agonist of the melanocortin receptor is MT-II. In another subclass of this class of the present invention, the combination of the present invention comprises a selective agonist of the melanocortin-4 receptor and a PDE-V inhibitor selected from the group consisting of sildenafil citrate, IC-351, M-54018, and M-54033. An especially preferred combination is a selective agonist of the melanocortin-4 receptor (MC-4R) and sildenafil citrate.

In another embodiment of the combination of the present invention, the second element of the combination is an alpha-adrenergic receptor antagonist. In a class of this embodiment of the present invention, the alpha-adrenergic receptor antagonist is selective for the alpha-2 receptor subtype. In a subclass of this class of the present invention, the alpha-2 receptor antagonist is yohimbine or delquamine. The efficacy of yohimbine in the treatment of psychogenic erectile dysfunction is reported in Lancet, pp. 42-43 (1987). Delquamine is an alpha adrenoreceptor antagonist, with a greater affinity for the alpha-2 receptor subtype [see A. Morales et al., "Oral and topical treatment of erectile dysfunction," Urol. Clin. North Am., 22: 879-885 (1995)].

In another subclass of this class of the present invention, the alpha-2 receptor antagonist is an arylquinolizine derivative disclosed in U.S. Patent Nos. 4,824,849 and 4,710,504, both of which are incorporated by reference herein in their entirety. In a subclass of this subclass of the present invention, the alpha-2 receptor antagonist is the benzofuroquinolizine analog, MK-912, disclosed in U.S. Patent No. 4,824,849. MK-912 represents 1',3'-dimethylspiro(1,3,4,5',6,6',7,12b-octahydro-2H-benzo[b]-furo[2,3-a]quinolizine)-2,4'-pyrimidin-2'-one and is a potent, orally active agent with a pharmacologic profile consistent with alpha-2 antagonism [see D.J. Pettibone, et al., "Pharmacological profile of a new potent and specific alpha2-adrenoceptor antagonist, L-657,743," Naunyn-Schmiederberg's Arch. Pharmacol., 336: 169-175 (1987)]. The effect of the drug on penile erections in healthy male volunteers was observed by B.J. Gertz et al. and reported in Clin. Pharmacol. Ther., 46: 566-575 (1989). An especially preferred combination is a selective agonist of the melanocortin-4 receptor (MC-4R) and MK-912.

The instant combination of an agonist of the melanocortin receptor and a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist is useful in the therapeutic treatment of erectile dysfunction. Although the

methods and compositions comprising drug combinations of the present invention are envisaged primarily for the treatment of male erectile dysfunction, they may also be useful for the treatment of female sexual dysfunction, including orgasmic dysfunction related to clitoral disturbances.

The combination of an agonist of the melanocortin receptor and a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist provides an unexpectedly superior effect in the treatment of erectile dysfunction. The combination provides for effective treatment of either psychogenic or organic erectile dysfunction in a greater percentage of the affected population than either element of the combination separately. The combination provides for a shorter onset of action and longer duration of action than either element of the combination separately. The combination also has fewer side effects and contraindications than either member of the combination separately.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following:

Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide and Valerate.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts.

The compounds of the present invention may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of erectile dysfunction with the compound specifically disclosed as an element of the combination or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

In the combination of the present invention, the agonist of the melanocortin receptor may be administered separately or in conjunction with the cyclic-GMP-specific phosphodiesterase inhibitor or the alpha-adrenergic receptor antagonist. In addition, the administration of one element of the combination of the present invention may be prior to, concurrent to, or subsequent to the administration of the other element of the combination.

The elements of the combination of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), buccal, nasal, vaginal, rectal, sublingual, or

topical (e.g.. ocular eyedrop) routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in the combination in an amount sufficient to produce the desired pharmacologic effect upon the process or condition of erectile dysfunction..

The pharmaceutical compositions containing the active ingredient suitable for oral administration may be in the form of discrete units such as hard or soft capsules, tablets, troches or lozenges, each containing a predetermined amount of the active ingredient; in the form of a dispersible powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; in the form of syrups or elixirs; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide a pharmaceutically elegant and palatable preparation.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compounds are admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods.

The excipients used may be for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents, such as corn starch or alginic acid; (3) binding agents such as starch, gelatin or acacia; and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients may be

1) suspending agents such as sodium carboxymethyl-cellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia;

(2) dispersing or wetting agents which may be

(a) a naturally-occurring phosphatide such as lecithin,

(b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate,

(c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol,

(d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or

(e) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide a palatable oral preparation. These compositions may be prepared by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as olive oil or arachis oils, or a mineral oil such as liquid paraffin or a mixture thereof. Suitable emulsifying agents may be (1) naturally-occurring gums such as gum acacia and gum tragacanth, (2) naturally-occurring phosphatides such as soybean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension or solution. The suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane- diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspension, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. The combination of this invention may also be administered in the form of suppositories for rectal administration. This composition can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols. Compositions for buccal, nasal or sublingual administration are also prepared with standard excipients well known in the art.

For topical administration the combination of this invention may be formulated in liquid or semi-liquid preparations such as liniments, lotions, applications; oil-in-water or water-in-oil emulsions such as creams, ointments, jellies or pastes, including tooth-pastes; or solutions or suspensions such as drops, and the like.

The dosage of the active ingredients in the compositions of this invention may be varied. However, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration and on the duration of the treatment. Dosage ranges in the combination for the melanocortin receptor agonist and cyclic-GMP-specific phosphodiesterase inhibitor or alpha-adrenergic receptor antagonist are approximately one tenth to one times the clinically effective ranges required to induce the desired erectogenic effect, respectively when the compounds are used singly. Generally, dosage levels of the melanocortin receptor agonist of between about 0.001 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250 and 500 milligrams of each of the active ingredients for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of each of the active ingredients, preferably, from about 1 mg to about 100 mg of each of the active ingredients. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Dosage levels of the cyclic-GMP-specific phosphodiesterase inhibitor or alpha-adrenergic receptor antagonist of between about 0.001 to 50 mg/kg of body weight daily, preferably about 0.005 to about 25 mg/kg per day, and more preferably about 0.01 to about 10 mg/kg per day are administered to a patient to obtain effective treatment of erectile dysfunction.

An especially preferred combination is that wherein the agonist of the melanocortin receptor is selective for the MC-4R subtype, the cyclic-GMP-specific phosphodiesterase inhibitor is the PDE-V inhibitor sildenafil citrate or IC-351, and the alpha-adrenergic receptor antagonist is the alpha-2 antagonist MK-912. In this especially preferred combination, dosage levels of each component are as noted above; however, it is even more preferred that the agonist of the MC-4R subtype be administered at a dosage rate of about 0.01 to about 10 mg/kg/day, especially about 0.05 to about 5.0 mg/kg/day, and more particularly about 0.1 to about 5 mg/kg/day, and that the PDE-V inhibitor, sildenafil citrate or IC-351, or the alpha-2 antagonist MK-912 be administered at a dosage level of about 0.001 to about 20 mg/kg/day,

especially about 0.005 to about 10 mg/kg/day, and more particularly about 0.01 to about 5 mg/kg/day.

More particularly illustrating the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Another example of the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

The test procedures used to measure the efficacy of the combination of the present invention to treat erectile dysfunction are described below in the following examples. These examples are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed.

EXAMPLE 1

Binding Assay.

The membrane binding assay is used to identify competitive inhibitors of 125I-α-NDP-MSH binding to cloned human melanocortin receptors expressed in L- or CHO- cells.

Cell lines expressing melanocortin receptors are grown in T-180 flasks containing selective medium of the composiiton: 1 L Dulbecco's modified Eagles Medium (DMEM) with 4.5 g L-glucose, 25 mM Hepes, without sodium pyruvate, (Gibco/BRl); 100 ml 10% heat-inactivated fetal bovine serum (Sigma); 10 ml 10,000 unit/ml penicillin & 10,000 µg/ml streptomycin (Gibco/BRl); 10 ml 200 mM L-glutamine (Gibco/BRl); 1 mg/ml Geneticin (G418) (Gibco/BRl). The cells are grown at 37°C with CO_2 and humidity control until the desired cell density and cell number are obtained.

The medium is poured off and 10 mls/monolayer of enzyme-free dissociation media (Specialty Media Inc.) is added. The cells are incubated at 37°C for 10 minutes or until cells slough off when flask is banged against hand.

The cells are harvested into 200 ml centrifuge tubes and spun at 1000 rpm, 4°C, for 10 min. The supernatant is discarded and the cells are resuspended in 5 mls/monolayer membrane preparation buffer having the composition: 10 mM Tris pH 7.2-7.4; 4 μg/ml Leupeptin (Sigma); 10 μM Phosphoramidon (Boehringer Mannheim); 40 μg/ml Bacitracin (Sigma); 5 μg/ml Aprotinin (Sigma); 10 mM Pefabloc (Boehringer Mannheim). The cells are homogenized with motor-driven dounce (Talboy setting 40), using 10 strokes and the homogenate centrifuged at 6,000 rpm, 4°C, for 15 minutes.

The pellets are resuspended in 0.2 mls/monolayer membrane prep buffer and aliquots are placed in tubes (500-1000 μl/tube) and quick frozen in liquid nitrogen and then stored at -80°C.

Test compounds or unlabelled NDP-α-MSH is added to 100 μL of membrane binding buffer to a final concentration of 1 μM. The membrane binding buffer has the composition: 50 mM Tris pH 7.2; 2 mM $CaCl_2$; 1 mM $MgCl_2$; 5 mM KCl; 0.2% BSA; 4 μg/ml Leupeptin (SIGMA); 10 μM Phosphoramidon (Boehringer Mannheim); 40 μg/ml Bacitracin (SIGMA); 5 μg/ml Aprotinin (SIGMA); and 10 mM Pefabloc (Boehringer Mannheim). One hundred μl of membrane binding buffer containing 10-40 μg membrane protein is added, followed by 100 μM ^{125}I-NDP-α-MSH to final concentration of 100 pM. The resulting mixture is vortexed briefly and incubated for 90-120 min at room temperature while shaking.

The mixture is filtered with a Packard Microplate 196 filter apparatus using Packard Unifilter 96-well GF/C filter with 0.1% polyethyleneimine (Sigma). The filter is washed (5 times with a total of 10 ml per well) with room temperature of filter wash having the composition: 50mM Tris-HCl pH 7.2 and 20 mM NaCl. The filter is dried, and the bottom sealed and 50 μl of Packard Microscint-20 is added to each well. The top is sealed and the radioactivity quantitated in a Packard Topcount Microplate Scintillation counter.

EXAMPLE 2

Functional assay.

Functional cell based assays are developed to discriminate melanocortin agonists and antagonists.

Cells (for example, CHO- or L-cells or other eukaryotic cells) expressing a human melanocortin receptor [see e.g. Yang-YK; Ollmann-MM; Wilson-BD; Dickinson-C; Yamada-T; Barsh-GS; Gantz-I; Mol. Endocrinol., 11: 274-80 (1997)] are dissociated from tissue culture flasks by rinsing with Ca and Mg free phosphate buffered saline (14190-136, Life Technologies, Gaithersburg, MD) and detached following 5 minutes incubation at 37°C with enzyme free dissociation buffer (S-014-B, Specialty Media, Lavellette, NJ). Cells are collected by centrifugation and resuspended in Earle's Balanced Salt Solution (14015-069, Life Technologies, Gaithersburg, MD) with additions of 10 mM HEPES pH 7.5, 5 mM $MgCl_2$, 1 mM glutamine and 1 mg/ml bovine serum albumin. Cells are counted and diluted to 1 to 5 x 10^6/ml. The phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine is added to cells to 0.6 mM.

Test compounds are diluted in dimethylsulfoxide (DMSO) (10^{-5} to 10^{-10} M) and 0.1 volume of compound solution is added to 0.9 volumes of cell suspension; the final DMSO concentration is 1%. After room temperature incubation for 45 min., cells are lysed by incubation at 100°C for 5 min. to release accumulated cAMP.

cAMP is measured in an aliquot of the cell lysate with the Amersham (Arlington Heights, IL) cAMP detection assay (RPA556). The amount of cAMP production which results from an unknown compound is compared to that amount of cAMP produced in response to alpha-MSH which is defined as a 100% agonist. The EC_{50} is defined as the compound concentration which results in half maximal stimulation, when compared to its own maximal level of stimulation.

Antagonist assay: Antagonist activity is defined as the ability of a compound to block cAMP production in response to alpha-MSH. Solution of test compounds and suspension of receptor containing cells are prepared and mixed as described above; the mixture is incubated for 15 min., and an EC_{50} dose (approximately 10 nM alpha-MSH) is added to the cells. The assay is terminated at 45 min. and cAMP quantitated as above. Percent inhibition is determined by comparing the amount of cAMP produced in the presence to that produced in the absence of test compound.

EXAMPLE 3

Rat Ex Copula Assay.

Sexually mature male Caesarian Derived Sprague Dawley (CD) rats (over 60 days old) are used with the suspensory ligament surgically removed to prevent retraction of the penis back into the penile sheath during the *ex copula* evaluations. Animals receive food and water *ad lib* and are kept on a normal light/dark cycle. Studies are conducted during the light cycle.

a) Conditioning to Supine Restraint for Ex Copula Reflex Tests. This conditioning takes ~ 4 days. Day 1, the animals are placed in a darkened restrainer and left for 15 - 30 minutes. Day 2, the animals are restrained in a supine position in the restrainer for 15 - 30 minutes. Day 3, the animals are restrained in the supine position with the penile sheath retracted for 15 - 30 minutes. Day 4, the animals are restrained in the supine position with the penile sheath retracted until penile responses are observed. Some animals require additional days of conditioning before they are completely acclimated to the procedures; non-responders are removed from further evaluation. After any handling or evaluation, animals are given a treat to ensure positive reinforcement.

b) Ex Copula Reflex Tests. Rats are gently restrained in a supine position with their anterior torso placed inside a cylinder of adequate size to allow for normal head and paw grooming. For a 400-500 gram rat, the diameter of the cylinder is approximately 8 cm. The lower torso and hind limbs are restrained with a non-adhesive material (vetrap). An additional piece of vetrap with a hole in it, through which the glans penis will be passed, is fastened over the animal to maintain the preputial sheath in a retracted position. Penile responses will be observed, typically termed *ex copula* genital reflex tests. Typically, a series of penile erections will occur spontaneously within a few minutes after sheath retraction. The types of normal reflexogenic erectile responses include elongation, engorgement, cup and flip. An elongation is classified as an extension of the penile body. Engorgement is a dilation of the glans penis. A cup is defined as an intense erection where the distal margin of the glans penis momentarily flares open to form a cup. A flip is a dorsiflexion of the penile body.

Baseline and or vehicle evaluations are conducted to determine how and if an animal will respond. Some animals have a long duration until the first response while others are non-responders altogether. During this baseline evaluation

latency to first response, number and type of responses are recorded. The testing time frame is 15 minutes after the first response.

After a minimum of 1 day between evaluations, these same animals are administered the test compound or combination at 20 mg/kg and evaluated for penile reflexes. All evaluations are videotaped and scored later. Data are collected and analyzed using paired 2 tailed t-tests to compare baseline and/or vehicle evaluations to drug- or combination- treated evaluations for individual animals. Groups of a minimum of 4 animals are utilized to reduce variability.

Positive reference controls are included in each study to assure the validity of the study. Animals can be dosed by a number of routes of administration depending on the nature of the study to be performed. The routes of administration include intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and intracerebral ventricular (ICV).

EXAMPLE 4

Models of Female Sexual Dysfunction

Rodent assays relevant to female sexual receptivity include the behavioral model of lordosis and direct observations of copulatory activity. There is also a urethrogenital reflex model in anesthetized spinally transected rats for measuring orgasm in both male and female rats. These and other established animal models of female sexual dysfunction are described in McKenna KE et al, A Model For The Study Of Sexual Function In Anesthetized Male And Female Rats, Am. J. Physiol. (Regulatory Integrative Comp. Physiol 30): R1276-R1285, 1991; McKenna KE et al, Modulation By Peripheral Serotonin Of The Threshold For Sexual Reflexes In Female Rats, Pharm. Bioch. Behav., 40:151-156, 1991; and Takahashi LK et al, Dual Estradiol Action In The Diencephalon And The Regulation Of Sociosexual Behavior In Female Golden Hamsters, Brain Res., 359:194-207, 1985.

EXAMPLE 5

As a specific embodiment of an oral composition of a combination of the present invention, 5 mg of a melanocortin agonist and 10 mg of a type V phosphodiesterase (PDE-V) inhibitor are formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

EXAMPLE 6

As another specific embodiment of an oral composition of a combination of the present invention, 2.5 mg of a melanocortin agonist and 5 mg of an alpha-2 receptor antagonist are formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the patient being treated for erectile dysfunction. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound or combination selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method for the treatment of erectile dysfunction which comprises administering to a human subject in need of such treatment an effective amount of an agonist of the melanocortin receptor in combination with an effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist.

2. The method of Claim 1 wherein said human subject is male.

3. The method of Claim 1 wherein said human subject is female.

4. The method of Claim 1 wherein the agonist of the melanocortin receptor is melanotan-II (MT-II).

5. The method of Claim 1 wherein the agonist of the melanocortin receptor agonist is selective for the melanocortin-4 receptor (MC-4R) subtype.

6. The method of Claim 1 wherein the inhibitor of the cyclic-GMP-specific phosphodiesterase is an inhibitor of the type V phosphodiesterase (PDE-V) isozyme.

7. The method of Claim 6 wherein the inhibitor of PDE-V is selected from the group consisting of:

a) sildenafil citrate,
b) IC-351,
c) M-54033,
d) M-54018, and
e) E-4010.

8. The method of Claim 7 wherein the inhibitor of PDE-V is sildenafil citrate.

9. The method of Claim 8 wherein the agonist for the melanocortin receptor is selective for the melanocortin-4 receptor subtype.

10. The method of Claim 1 wherein the alpha-adrenergic receptor antagonist is selective for the alpha-2 receptor subtype.

11. The method of Claim 10 wherein the alpha-2 receptor antagonist is yohimbine, delquamine, or MK-912.

12. The method of Claim 11 wherein the alpha-2 receptor antagonist is MK-912.

13. The method of Claim 12 wherein the agonist for the melanocortin receptor is selective for the melanocortin-4 receptor subtype.

14. A pharmaceutical composition for the treatment of erectile dysfunction which comprises a pharmaceutically acceptable carrier, a therapeutically effective amount of an agonist of the melanocortin receptor and a therapeutically effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist.

15. The pharmaceutical composition of Claim 14 wherein the inhibitor of the cyclic-GMP-specific phosphodiesterase is an inhibitor of the type V phosphodiesterase (PDE-V) isozyme and the alpha-adrenergic receptor antagonist is selective for the alpha-2 receptor subtype.

16. The pharmaceutical composition of Claim 15 wherein the alpha-2 receptor antagonist is MK-912.

17. The pharmaceutical composition of Claim 15 wherein the PDE-V inhibitor is selected from the group consisting of:

a) sildenafil citrate,
b) IC-351,
c) M-54018,
d) M-54033, and
e) E-4010.

18. The pharmaceutical composition of Claim 17 wherein the PDE-V inhibitor is sildenafil citrate.

19. The pharmaceutical composition of Claim 14 wherein the agonist of the melanocortin receptor is selective for the melanocortin-4 receptor (MC-4R) subtype.

20. The use of an agonist of the melanocortin receptor in combination with a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist for the preparation of a medicament useful to treat erectile dysfunction.

21. The use of Claim 20 wherein the inhibitor of the cyclic-GMP-specific phosphodiesterase is an inhibitor of the type V phosphodiesterase (PDE-V) isozyme.

22. The use of Claim 21 wherein the inhibitor of the type V phosphodiesterase isozyme is sildenafil citrate.

23. The use of Claim 20 wherein the alpha-adrenergic receptor antagonist is MK-912.

24. The use of Claim 20 wherein the agonist of the melanocortin receptor is selective for the melanocortin-4 receptor (MC-4R) subtype.

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(54) Title: METHODS AND COMPOSITIONS FOR TREATING ERECTILE DYSFUNCTION

(57) Abstract: The present invention provides for a method for the treatment of erectile dysfunction in a male or female human subject in need of such treatment comprising administration of a therapeutically effective amount of an agonist of the melanocortin receptor in combination with a therapeutically effective amount of a cyclic-GMP-specific phosphodiesterase inhibitor or an alpha-adrenergic receptor antagonist. Further, the present invention provides for pharmaceutical compositions useful in the methods of the present invention, as well as a method of manufacture of a medicament useful for treating erectile dysfunction.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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US CL : 514/11
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)

U.S. : 514/11

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 practicable, search terms used)

WEST CAS/STN WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	WO 99/30697 A2 (PFIZER PRODUCTS INC.) 24 June 1999 (24.06.99), see entire document (kit of sildenafil and E.G. Yohimbine).	1-24
Y, P	WO 99/59584 A1 (SCHERING CORPORATION) 25 November 1999 (25.11.99), see entire document (kit of sildenafil, Yohimbine, Phentocamine, etc.).	1-24
Y, P	WO 99/60985 A2 (SAINT LOUIS UNIVERSITY) 02 December 1999 (02.12.99), see entire document (mixture of Yohimbine, phentolamine, papaverine).	1-24

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"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
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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/05711

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	WO 99/30718 A2 (SCOTT) 24 June 1999 (24.06.99), see entire document (impotence combination of prostaglandins, anaesthics instead of "VIAGRA" (SILDENAFIL).	1-24
Y	WO 96/16657 A1 (PFIZER LIMITED) 06 June 1996 (06.06.96), see entire document (sildenafil-like pyrazo pyrimioinones, or acternatively, erectile dysfunction combinations of papaverine, phentolamine and prostaglanoins).	1-24
Y	US 6,037,346 A (DOHERTY, JR. et al.) 14 March 2000 (14.03.00), see entire document (kit of sildenafil and yohimbines).	1-24
Y, P	US 6,007,824 A (DUCKETT et al.) 28 December 1999 (28.12.99), see entire document ("VIAGRA" or synergistic natural sexual dysfunction agent combinations).	1-24
Y, P	US 5,994,294 A (GARVEY et al.) 30 November 1999 (30.11.99), see entire document (erectile dysfunction combination of yohimbine and phentolamines).	1-24
Y, P	US 5,962,528 A (SCOTT) 05 October 1999 (05.10.99), see entire document (impotence treating combination of prostaglandins).	1-24
Y, P	US 5,932,538 A (GARVEY et al.) 03 August 1999 (03.08.99), see entire document (erectile combination of yohimbine and pitewtolamine).	1-24
Y	US 5,731,339 A (LOWREY) 24 March 1998 (24.03.98), see entire document (impotence combination of yohimbine and phentolamine).	1-24
Y	US 5,567,706 A (GAVRAS) 22 October 1996 (22.10.96), see entire document (combination of yohimbine and known impotence adrenoceptor agents).	1-24
Y	US 5,576,290 A (HADLEY) 19 November 1996 (19.11.96), see entire document.	1-24
Y, E	US 6,051,555 A (HADLEY) 18 April 2000 (18.04.00), see entire document.	1-24

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/05711

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94/28902 A1 (PFIZER LIMITED) 22 December 1994 (22.12.94), see entire document.	1-24
Y, P	WO 99/66933 A1 (NEW MILLENNIUM PHARMACEUTICALS RESEARCH, INC.) 29 December 1999 (29.12.99), see entire document.	1-24
Y, P	EP 0 960 621 A2 (PFIZER INC.) 01 December 1999 (01.12.99), see entire document.	1-24
Y, P	WO 97/03675 A1 (LABORATOIRE GLAXO WELLCOME S.A.) 06 February 1997 (06.02.97), see entire document.	1-24

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(54) Title: TREATMENT OF FEMALE AROUSAL DISORDER

(57) Abstract

A method of treating female arousal disorder (FAD) 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.

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TREATMENT OF FEMALE AROUSAL DISORDER

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of provisional patent application Serial No. 60/132,129, filed April 30, 1999.

FIELD OF THE INVENTION

The present invention relates to highly selective phosphodiesterase (PDE) enzyme inhibitors and to their use to treat female arousal disorder (FAD), also known as female sexual arousal disorder (FSAD). In particular, the present invention relates to potent inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase type 5 (PDE5) that, when administered as a pharmaceutical product, are useful for the treatment of FAD.

BACKGROUND OF THE INVENTION

Female sexual dysfunction (FSD) is a highly prevalent condition (R.T. Micheal et al., *Sex in America*, Little Brown, Boston, MA (1994)). However, in contrast to the overwhelming interest in treatment of male erectile dysfunction (MED) (Feldman et al. 1994, NIH Consensus Development Panel on Impotence 1993, Rosen et al. 1997; Sildenafil Study Group 1998), relatively little attention has been paid to sexual problems in women. There are few studies of the physiological process of the female sexual response, and there are few effective treat-

ments available to women for sexual problems. Furthermore, a barrier to research and development in this area has been the lack of established diagnostic classifications, or of established endpoints, for testing new drugs in clinical trials for the treatment of FSD.

FSD has been used as a "catchall" phrase to include a variety of sexual disorders in woman including sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorders, vaginismus, dyspareunia, trauma from sexual contact, sexual inhibition, sexual panic disorders, childhood sexual abuse, and sexual addiction or compulsive behavior. From the multitude of disorders, The American Psychiatric Association, *Diagnostic and Statistical Manual, Mental Disorders, Ed. 3*, Washington, DC, APA (1980) and the International Classification of Diseases (World Health Organization) have identified four major categories of female sexual dysfunction: (1) sexual desire disorders, (2) sexual arousal disorders, (3) orgasmic disorders, and (4) sexual pain disorders. Each of these categories can be further sub-typed as follows: lifelong versus acquired type; generalized versus situational type; etiologic classification (e.g., organic, psychogenic, mixed, unknown).

Sexual desire disorders are defined by the following two diagnoses. Hypoactive Sexual Desire Disorder (HSDD) is the persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts and/or desire for, or receptivity to, sexual activity, which causes personal distress. Sexual Aversion Disorder is the persistent or recurrent

phobic aversion to, and avoidance of, sexual contact with a sexual partner, which causes personal distress.

Sexual arousal disorders are defined as a recurrent inability to attain, or maintain until completion of sexual activity, an adequate lubrication/swelling response of sexual excitement. The arousal response consists of vasocongestion in the pelvis, vaginal lubrication, and expansion and swelling of external genitalia. The disturbance must cause marked distress or interpersonal difficulty.

Orgasmic disorders are defined as the persistent or recurrent difficulty, delay in, or absence of, attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress.

Sexual pain disorders are defined by the following three diagnoses. Dyspareunia is a recurrent or persistent genital pain associated with sexual intercourse. Vaginismus is a recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress. Noncoital Sexual Pain Disorder is a recurrent or persistent genital pain induced by noncoital sexual stimulation.

Unfortunately, use of the term "female sexual dysfunction" as a catchall phrase to broadly encompass all disorders fails to distinguish the significant clinical and physiological differences between these disorders, and offers little guidance to the attending physician with respect to how to

properly diagnose and prescribe pharmacological treatment. Because pharmacological treatment is not uniformly effective against all varieties of female sexual dysfunction, there remains a need in the art to identify which pharmacological therapy is useful to treat which sexual disorder.

Place et al. U.S. Patent No. 5,877,216 discloses a method of treating sexual dysfunction in a female individual by administering a pharmaceutical formulation containing a selected vasodilating agent to the vagina and/or vulvar area of the individual undergoing treatment. The application is directed to prostaglandins, but additional vasodilation agents that are useful in conjunction with the invention are disclosed and include, inter alia, phosphodiesterase inhibitors. Phosphodiesterase inhibitors are not further defined. Neither PDE5 inhibitors or their use to treat female arousal disorder are disclosed.

EP 0 702 555 describes the method of treating male erectile dysfunction with a PDE inhibitor and particularly a PDE5 inhibitor. The patent application further suggests that a PDE inhibitor may be used for female sexual dysfunction, particularly orgasmic dysfunction related to clitoral disturbances. Neither PDE inhibitor, PDE5 inhibitor, nor female sexual dysfunction are defined further except by reference to compounds specifically disclosed and referenced to orgasmic dysfunction.

Sildenafil citrate (sildenafil, sold under the trademark VIAGRA®), is a known PDE5 inhibitor, and has been shown to facilitate erectile function

in men suffering from MED. In particular, sildenafil amplifies the effect of central and peripheral physiologic signals resulting in cyclic guanosine monophosphate (cGMP) mediation of corpus cavernosum smooth muscle relaxation, leading in turn to vasodilation and blood pooling which produces an erection. While there are obvious external anatomical differences between male and female external genitalia, there also is a recognized tissue homology. In addition, there is accumulating evidence of analogous physiological responses (for example, relaxation of clitoral corpus cavernosum and genital vasodilation, K. Park et al., *Biochem. Biophys. Res. Commun., 249(3)*:612-617 (1998)), in female sexual tissue. However, the clinical significance of a response in female sexual tissue, and what, if any, disorder this response correlates to has not been disclosed.

While sildenafil is approved for use in males, several publications have referenced clinical studies in women. M. Fava et al., in *Psychother. Psychosom., 67(6)*: 328-31 (1998), studied the effects of sildenafil on antidepressant-induced sexual dysfunction in 14 depressed patients (9 men and 5 women). Antidepressant-induced sexual dysfunction is generally characterized by a lack of desire (sexual desire disorder) and delayed orgasm and anorgasmia (orgasmic disorder), but also may include arousal difficulties, H.G. Nurnberg et al., *J. Clin. Psychiatry, 60(1)*, 33-35 (1999). The study reports a statistically significant improvement in all domains of sexual functioning with a 69% rate of patients reporting improvement. However, the study

fails to indicate the response by gender (9 out of 14 patients were men). In addition, the study was not placebo controlled, and fails to correct the data for a placebo effect. The authors could not "rule out the possibility that clinical improvements in sexual functioning in our patients may be the result of nonspecific placebo-like effects." These shortcomings in the study leave a person skilled in the art unable to draw conclusions with respect to the efficacy of using sildenafil in treating sexual desire disorder and anorgasmia, and the study offers no motivation to study its usefulness to treat female arousal disorder.

Kaplan et al., in *Urology 53(3)*:481-6 (1999), studied the safety and efficacy of sildenafil in postmenopausal woman with self-described sexual dysfunction. The form of sexual dysfunction being treated was not further defined or characterized. Sildenafil was studied in thirty-three postmenopausal women with sexual dysfunction. The study used the Female Sexual Function Index, which contains one question on vaginal dryness, with other questions focused on sexual desire, pain, satisfaction, and clitoral sensation. The study was not directed to arousal disorder. Six patients reported significant improvement in therapeutic response. Improvement in lubrication and clitoral sensation improved by 0.54 (23.2%) and 0.67 (31.3%), respectively. Clitoral discomfort and "hypersensitivity" occurred in 7 woman (3 of whom withdrew from the study). While the authors concluded that sildenafil is well tolerated in postmenopausal women, they also

concluded that sildenafil did not significantly improve overall sexual function.

Finally, sildenafil was studied for the treatment of iatrogenic serotonergic antidepressant medication-induced sexual dysfunction in four patients (two men, two woman) by H.G. Nurnberg et al. in *J. Clin. Psychiatry, 60(1)*:33-5 (1999). The antidepressant medication-induced dysfunction is reported as erectile dysfunction and anorgasmia (orgasmic dysfunction). Female arousal disorder is not disclosed. The study reports that all four patients responded positively, however, the authors reserve drawing conclusions on the usefulness of sildenafil in treating antidepressant induced sexual dysfunction pending randomized placebo-controlled studies.

Thus, the limited studies of sildenafil to treat female sexual dysfunction have focused primarily on antidepressant induced sexual dysfunction (primarily indicative of orgasmic dysfunction and sexual desire dysfunction) and have lead to inconclusive results.

It has been discovered that the compounds of structural formula (I) are highly effective in treating female arousal disorders. Accordingly, the present invention provides methods of treating female arousal disorder, which comprise administering a compound of formula (I) to a patient in need thereof. Such methods are novel and unsuggested by the prior art.

SUMMARY OF THE INVENTION

The present invention provides a method of treating female arousal disorder (FAD) in a female patient, which comprises orally administering to said patient a pharmaceutically effective amount of an agent that inhibits cyclic guanosine 3'5'-monophosphate specific phosphodiesterase type 5.

The invention further provides a method of treating a female patient suffering from female arousal disorder comprising inhibiting cyclic guanosine 3'5'-monophosphate specific phosphodiesterase type 5 a sufficient amount to enhance genital and vaginal blood flow in said patient.

The invention also provides for the use of a PDE5 inhibitor to treat female arousal disorder.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of the present invention, as disclosed and claimed herein, the following terms are defined as follows:

The phrase "female arousal disorder" (FAD) as used herein refers to a condition characterized by an inability or delay in becoming aroused, or a failure to maintain an aroused state. Symptoms of the condition include a lack of genital or somatic responses such as throbbing, tingling, lubrication, and the subjective feelings of excitement and arousal. It is a subtype of female sexual dysfunction, and is largely independent of desire and orgasm. Patients likely to respond to therapy have experienced successful sexual experiences and have

acquired the disorder through any number of organic factors, psychogenic factors, or other unknown reasons.

The term "IC_{50}" is the measure of potency of a compound to inhibit an enzyme, e.g., the PDE5 enzyme (PDE5). The IC_{50} value 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 known *in vitro* methodology generally described in Y. Cheng et al., *Biochem Pharmacology 22*:3099-108 (1973).

The term "inhibiting" or "inhibits" refers to blocking the enzymatic activity of cyclic guanosine 3'5'-monophosphate specific phosphodiesterase type 5 to a sufficient degree to enhance genital and vaginal blood flow and produce a clinically significant response.

The phrase "orally administering" refers to the administration of a PDE5 inhibitor by any number of recognized oral dosage forms, including liquid dosage forms, tablets, capsules, gel-caps, and the like.

The term "PDE5 inhibitor" means an agent that inhibits cyclic guanosine 3'5'-monophosphate specific phosphodiesterase type 5 (PDE5) enzyme and has an IC_{50} value against PDE5 of 10 nM or less.

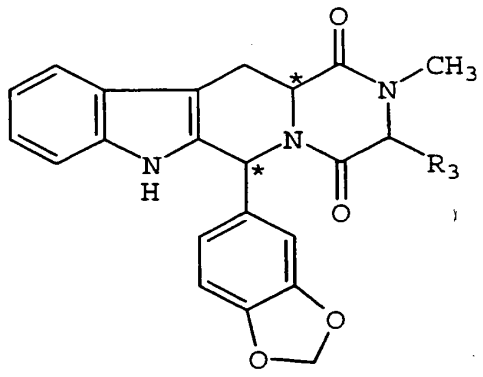
The term "a pharmaceutically effective amount" represents an amount of a compound that is capable of inhibiting PDE5 in females and causes in clinically significant response. The clinical response includes an improvement in the condition treated or in the prevention of the condition. The

particular dose of the compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case, including the compound administered, the particular condition being treated and similar considerations.

The term "agent" refers to a chemical compound suitable for pharmaceutical use.

As noted above, the present invention provides the use of a compound of formula (I) that inhibits cyclic guanosine 3'5'-monophosphate specific phosphodiesterase type 5 for treating female arousal disorder (FAD). The method comprises orally administering a pharmaceutical formulation comprising a PDE5 inhibitor to the female patient.

The compounds of structural formula (I), and their methods of manufacture, are disclosed in Daugan U.S. Patent No. 5,859,006 and Daugan et al. U.S. Patent No. 5,981,527, each incorporated herein by reference.



(I)

and salts and solvates (e.g., hydrates) thereof, wherein R^3 is hydrogen or methyl.

The compounds of structural formula (I) include:

(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;

physiologically acceptable solvates thereof, and mixtures thereof.

Compounds of structural formula (I), and their preparation, are disclosed in U.S. Patent No. 5,859,006, incorporated herein by reference, and are particularly advantageous due to their selectivity for PDE5.

The methods of the present invention can be carried out by incorporating a compound of formula (I) into a suitable formulation and administering a pharmaceutically acceptable amount of the

PDE5 inhibitor to a patient in need thereof. Any pharmaceutically acceptable excipients for oral use are suitable for preparation of such formulations. Suitable pharmaceutical formulations include those described in WO 96/38131. Preferably, the formulations comprise generally recognized as safe pharmaceutical excipients such as lactose, microcrystalline cellulose, starch, calcium carbonate, magnesium stearate, stearic acid, talc, and colloidal silicon dioxide.

The formulations 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 and compression into tablets, with or without film coating; dry blending followed by compression into tablets, with or with 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 PDE5 inhibitor is administered orally in an amount that is capable of inhibiting PDE5 in females and causing a clinically significant response. The clinical response includes an improvement in the condition treated or in the prevention of the condition. The particular dose of the compound administered according to this invention, of

course, is determined by the particular circumstances surrounding the case, including the compound administered, the severity of the condition being treated, and similar considerations. Preferably, the dose is 1 to 400 mg, and more preferably a 1 to 20 mg dose, as needed, up to the total dose for the day. Preferably, the dose administered is 5 to 20 mg/day, and most preferably a 10 mg dose is administered once per day, as needed.

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

Preparation 1

(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 was prepared as described in U.S. Patent No. 5,859,006, and formulated into 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), 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.

Component	Formulations (mg per tablet)	
Agent (PDE5 inhibitor)	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	0.05
Magnesium stearate	1.25	1.25
Total core subtotal (film coat Opadry OY-S-7322)	250.00	250.00

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 can 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.

Preparation 2

The following batch formula is used in preparing the finished dosage form.

Ingregient	Quantity (mg)
Granulation	
Agent (PDE5 inhibitor)	10.00
Lactose monohydrate	153.80
Lactose monohydrate (Spray Dried)	25.00
Hydroxypropylcellulose	4.00
Croscarmellose sodium	9.00
Hydroxypropylcellulose	1.75
Sodium lauryl sulfate	0.70
Outside Powders	
Microcrystalline cellulose	37.50
Croscarmellose sodium	7.00
Magnesium stearate	1.25
Total	250 mg
Film Coat (approximately)	11.25 mg

Purified Water, USP is used in the manufacture of these tablets. 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 follows:

The drug and excipients to be granulated are security sieved. The active agent is dry blended with lactose monohydrate (spray dried), hydroxypropyl cellulose, croscarmellulose sodium, and lactose monohydrate. The resulting powder blend is granulated with an aqueous solution of hydroxypropyl cellulose and sodium lauryl sulfate using a Powerex high shear granulator. Additional water may be added to reach the desired endpoint. A mill may be used to delump the wet granulation and facilitate drying. The wet granulation is dried using either a fluid bed dryer or drying oven. Once the material is dried, it may 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 may 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 is then 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

may be lightly dusted with talc to improve tablet handling characteristics.

Example 1

FAD clinical studies

The use of an agent that inhibits PDE5 for the treatment of female arousal disorder is demonstrated in a clinical study assessing the physiological effect of the agent in enhancing genital blood flow in the presence of sexual stimulation and measuring clinical endpoints for assessing improvement in arousal. This study is a double-blinded placebo controlled crossover study in normal, healthy woman. Patients are administer study drug (at doses from 1 to 20 mg) or placebo. After administration, the patients are exposed to a variety of stimuli including visual, tactile, or olfactory stimuli. Endpoints assessed include altered vaginal blood flow as measured using a vaginal photoplethysmography amplitude (VPA). Subjective endpoints of genital response (throbbing, tingling, and arousal) are measured.

Example 2

FAD clinical studies

The use of an agent that inhibits PDE5 for the treatment of female arousal disorder is demonstrated in a clinical study assessing the physiological effect of the agent in enhancing genital blood flow in the presence of sexual stimulation and measuring clinical endpoints for assessing improve-

ment in arousal. The study is conducted in women suffering from mild to moderate acquired female arousal disorder. The study is a double-blinded, placebo controlled study in 200 woman. In the study, subjects receive either drug or placebo at a doses of 5 mg, 10 mg, or 20 mg (daily or on demand as needed) for up to three months. Endpoints of the study are measured using a validated questionnaire (Female Sexual Functioning Index) which assesses five domains, with one domain specifically focused on arousal. This questionnaire is given at baseline and at each monthly visit. In addition, sexual experience is evaluated using an event diary focusing on arousal and sexual satisfaction.

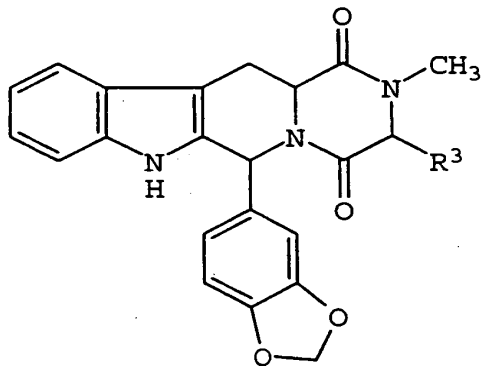
The present invention is based on the discovery that successful therapy is achieved through (1) proper diagnosis of patients suffering from female arousal disorder, which is a distinct subset of patients suffering from female sexual dysfunction; and (2) the use of a PDE5 inhibitor having a potency (i.e., an IC_{50} versus PDE5) of 10 nM or less. Patients who suffer from female arousal disorder and respond to the methods described herein are those who have acquired an inability or delay in becoming aroused, or a failure to maintain an aroused state. Symptoms of the condition includes a lack of somatic responses such as throbbing, tingling, lubrication and the subjective feelings of excitement or arousal. Woman who suffer from female arousal disorder have experienced successful sexual experiences and have acquired the disorder through any number of organic factors, psychogenic factors or other unknown reasons. Significantly, Applicants

have found that the desire is not a requisite for the treatment of arousal. Whether desire is present or not does not influence the diagnosis and treatment of female arousal disorder. However, successful treatment of FAD leads to better sexual experiences, which in turn can lead to improvement in desire and orgasm.

The principles, preferred embodiments, and modes of operation of the present invention have been described in the foregoing specification. The invention that is protected herein, however, should not be construed as limited to the particular forms disclosed, because they are to be regarded as illustrative rather than restrictive.

WHAT IS CLAIMED IS:-

1. A method of treating female arousal disorder in a female patient comprising orally administering to said patient a pharmaceutically effective amount of a compound having the structural formula



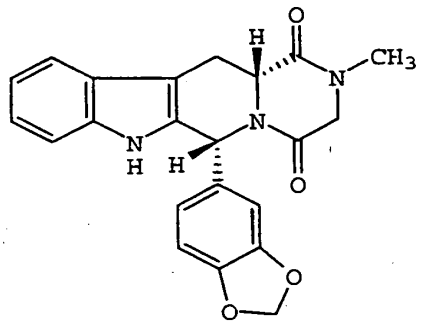
and salts and solvates thereof,

wherein R^3 is hydrogen or methyl.

2. The method of claim 1 wherein the female arousal disorder is acquired female arousal disorder.

3. The method of claim 1 wherein the compound is selected from the group consisting 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;
(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;
physiologically acceptable salts and solvates thereof; and mixtures thereof.

4. The method of claim 1 wherein the compound has the structure



5. Use of an inhibitor of cyclic guanosine 3'5'-monophosphate specific phosphodiesterase type 5 in the preparation of a medicament for the treatment of female arousal dysfunction.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/11128

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/395
US CL :514/250

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)

U.S. : 514/250

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

NONE

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

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,981,527 A (DAUGAN et al.) 09 November 1999, see abstract and column 2, lines 36-56.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DWAYNE C. JONES Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/11128

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

REGISTRY, CA, USPATFULL, WPIDS, TOXLIT, TOXLINE, BIOSIS, MEDLINE search terms include: phosphodiesterase(5a)inhibitor##, female(5a)arousal# or sex or sexual(6a)disorder#, pde5 or pde 5 and inhibit#####

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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.

WO 01/80860 A2

(54) Title: DAILY TREATMENT FOR ERECTILE DYSFUNCTION USING A PDE5 INHIBITOR

(57) Abstract: The present invention relates to 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 10 mg unit dosage are useful for the treatment of sexual dysfunction by daily administration of the PDE5 inhibitor. The articles of manufacture described herein are characterized by PDE5 inhibition, and accordingly, provide a benefit in therapeutic areas where inhibition of PDE5 is desired, especially erectile dysfunction, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes and with an improvement of vascular conditioning.

DAILY TREATMENT FOR ERECTILE DYSFUNCTION USING A PDE5 INHIBITOR

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Serial No. 09/558,911, filed April 26, 2000, which 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 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 are useful for the treatment of sexual dysfunction.

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*:285A (1993)). Thus, PDE5 is an attractive target in the treatment of sexual dysfunction (Murray, *DN&P 6(3)*:150-56 (1993)).

A pharmaceutical product that provides a PDE5 inhibitor is currently available, and is 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. 128-143 (1997)), and as 3.9 nM (Boolell et al., *Int. J. of Impotence Res., 8* p. 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, problems in the treatment of erectile dysfunction (ED) still exist. First, ED therapy using sildenafil is based on an on-demand or PRN therapy. "On demand" dosing is defined as an acute administration of a drug for treating erectile dysfunction prior to expected sexual activity. The user therefore must plan ahead, and, as presently labeled, ingest a relatively large oral dose (i.e.,

at least 25 mg) of sildenafil at least one hour prior to engaging in sexual activity. The onset of beneficial effects may be delayed when sildenafil is administered with a meal.

Second, the relatively large on-demand dose of sildenafil results in significant adverse side effects, including facial flushing (10% incidence rate). Thus, even with the availability of sildenafil, there remains a need to identify improved pharmaceutical products that are useful and more convenient in treating sexual dysfunction.

The present invention provides an article of manufacture for human pharmaceutical use, comprising a package insert, a container, and an oral dosage form comprising a PDE5 inhibitor at unit dosages between about 1 and about 10 mg/dosage form. The package insert provides a dosing regimen characterized by a chronic administration of the PDE5 inhibitor. The beneficial effects of a chronic dosing regimen were observed in clinical studies and through the discovery that the administration of a PDE5 inhibitor improves or conditions the vasculature such that the corpus cavernosum smooth muscle tissue responds to therapy at doses below that required to yield the same response with on-demand or acute therapy. The benefits of a low, chronic administration of a PDE5 inhibitor include improved vascular response to cGMP-stimulated relaxation in the corpus cavernosum smooth muscle tissue, lower toxicity attributed to a lower dose of PDE5 inhibitor, and a return to normalcy, i.e., the patient is not required to plan sexual activity around administration of the PDE5 inhibitor. The

dosing regimen of the present invention allows a spontaneity of sexual activity desired by the patient.

SUMMARY OF THE INVENTION

The present invention provides an article of manufacture for human pharmaceutical use, comprising a package insert, a container, and an oral dosage form comprising about 1 to about 10 mg of a PDE5 inhibitor per dosage form for chronic, and preferably daily, dosing.

The present invention further provides a method of treating male erectile dysfunction comprising administering to a patient in need thereof an oral dosage form containing about 1 to about 10 mg of a PDE5 inhibitor, chronically, up to a total dose of 10 mg/day.

The present invention further provides a method of improving the relaxant response in corpus cavernosum smooth muscle tissue, which comprises chronically administering a dose of 1 mg/day to 10 mg/day of a PDE5 inhibitor.

The present invention provides an article of manufacture for human pharmaceutical use, comprising a package insert, a container, and an oral dosage form comprising about 1 to about 10 mg of a selective PDE5 inhibitor, said package insert providing for a chronic administration of the PDE5 inhibitor to treat a patient suffering from erectile dysfunction.

The present invention provides an article of manufacture for human pharmaceutical use,

comprising a package insert, a container, and an oral dosage form of a selective PDE5 inhibitor; said package insert providing for a chronic administration of the PDE5 inhibitor to treat a patient suffering from erectile dysfunction.

The present invention further provides an article of manufacture for human pharmaceutical use comprising:

(a) an oral dosage form comprising about 1 to about 10 mg of a PDE5 inhibitor having an IC_{50} less than 10 nM, and a sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages;

(b) a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof, and has a chronic dosing regimen of about 1 to about 10 mg/day, wherein the chronic dosing regimen improves vascular conditioning; and

(c) a container.

The present invention further provides an article of manufacture for human pharmaceutical use comprising:

(a) an oral dosage form comprising about 1 to about 10 mg of a PDE5 inhibitor having

(i) an IC_{50} less than 10 nM, and

(ii) a sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages;

(b) a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof, and has a chronic dosing regimen of about 1 to about 10 mg/day, wherein

the chronic dosing regimen improves vascular conditioning; and

(c) a container.

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 recog-

nized by those skilled in the art to include such forms as liquid formulations, tablets, capsules, and gelcaps.

The terms "day" and "daily" refer to the administration of the product one or more times, generally one to three times, still more preferably one time, per about 24-hour period. "About 24-hour period" refers to a time span of about 20 to about 28 hours.

The term "chronic or chronically" refers to the regular administration of the product in intervals unrelated to the onset of sexual activity. To receive the full benefit of the present invention, chronic administration generally refers to regular administration for an extended period, preferably daily for three or more days, and still more preferably daily as long as the patient suffers from erectile dysfunction (in the absence of therapy). The term "chronic" administration encompasses other regimens in addition to daily dosing. For example, chronic administration encompasses administration of a sustained release formulation that provides sufficient PDE5 inhibitor on a regular basis and unrelated to the onset of sexual activity. Contrary to acute or on-demand administration, chronic administration does not link the administration of the PDE5 inhibitor to the onset of sexual activity (e.g., one hour prior to intercourse).

The term "PDE5 inhibitor" refers to compounds having an IC_{50} value for inhibition of PDE5 of less than 10 nM. Preferred PDE5 inhibitors are selective for PDE5 inhibition, such as those having:

(1) an IC_{50} value for the inhibition of PDE5 at least 100 times less than the IC_{50} value for the inhibition of PDE6;

(2) an IC_{50} value for the inhibition of PDE5 at least 1,000 times less than the IC_{50} value for the inhibition of PDE1c; and

(3) an IC_{50} value for the inhibition of PDE5 less than 10 nM.

PDE5 inhibitors vary significantly in chemical structure, and their use in the present invention is not dependent on chemical structure, but rather on the potency parameters disclosed herein.

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

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

As previously stated, the present invention is directed to an article of manufacture for human pharmaceutical use, comprising a package insert, a container, and a dosage form comprising about 1 to about 10 mg of a PDE5 inhibitor per unit dosage form. A PDE5 inhibitor useful in the present invention is a PDE5 inhibitor having an IC_{50} value for PDE5 inhibition of less than 10 nM, and is sufficiently bioavailable to be effective in about 1 to about 10 mg unit dosages.

Preferred PDE5 inhibitors selectively inhibit PDE5 versus PDE6 and PDE1c. Selectivity is quantified by the differential in IC_{50}. The differential is expressed as a PDE6/PDE5 ratio of IC_{50} values, i.e., the ratio of the IC_{50} value versus PDE6

to the IC_{50} value versus PDE5 (PDE6/PDE5) is greater than 100, more preferably greater than 300, and most preferably greater than 500.

Similarly, the ratio of IC_{50} value versus PDE1c to IC_{50} value versus PDE5 (PDE1c/PDE5) is greater than 1000. Preferred PDE5 inhibitors have a greater than 3,000 fold differential between the inhibition of PDE5 and PDE1c, more preferably greater than a 5,000 fold differential between IC_{50} value versus PDE5 and PDE1c. The potency of the inhibitor, as represented by the IC_{50} value versus PDE5, is less than 10 nM, preferably less than 5 nM, more preferably less than 2 nM, and most preferably less than 1 nM.

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 present article of manufacture indicates that the PDE5 inhibitor is useful in the treatment of conditions wherein inhibition of PDE5 is desired, particularly sexual dysfunction, and particularly male erectile dysfunction and female sexual arousal disorder.

The package insert also provides instructions to administer one or more about 1 to about 10 mg unit dosage forms, chronically, and preferably daily, for at least three days, up to a maximum total dose of 10 mg per day. The dose administered typically is about 1 to about 10 mg/day, more pref-

erably about 2 to about 10 mg, and most preferably an about 5 mg to about 10 mg dosage form administered daily.

Because a presently claimed article of manufacture provides a chronic dosing regimen that is more efficacious than the equivalent on-demand or acute dose, incidences of side effects are notably reduced. Therefore, the preferred article of manufacture provides a package insert having reported 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 present 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 10 mg of a PDE5 inhibitor. Any pharmaceutically acceptable excipients for oral use are suitable for preparation of such dosage forms. Suitable pharmaceutical dosage forms include copre-

cipitate 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 the PDE5 inhibitor, but rather contains a solid PDE5 inhibitor 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 oral dosage form also can be in the form of sustained release formulation that chronically provides about 1 to about 10 mg/day of the PDE5 inhibitor to an individual over the course of a few to several days.

The present invention is based on detailed experiments and clinical trials, and the unexpected observations that sexual dysfunction can be treated using a chronic, low dose of a PDE5 inhibitor having an IC_{50} value for inhibition of PDE5 less than 10 nM.

A chronic, and preferably daily, dosing regimen of about 1 to about 10 mg of a PDE5 inhibitor also provides other benefits including (a) spontaneity in sexual relations, (b) unexpected efficacy for such a low oral dose of PDE5 inhibitor, including an observation of a greater response to the PDE5 inhibitor from a lower chronic PDE5 inhibitor dose than to the currently labeled 25 mg acute, on-demand dose of sildenafil, and (c) no to low adverse effects attributed to the selective PDE5 inhibitor and a low dose.

Overall, it has been demonstrated that chronic dosing of a PDE5 inhibitor having the properties enumerated above provides the same or improved efficacy at about 1 mg to 10 mg than a higher acute on-demand dosage presently administered. The enhanced efficacy demonstrated by low daily dosing of a PDE5 inhibitor in treating erectile dysfunction is not dependent on drug accumulation, but rather results from improved vascular responsiveness when the PDE5 inhibitor is present continuously, or essentially continuously, in plasma.

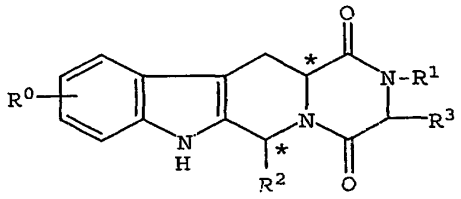
The "vascular conditioning" effect has not been demonstrated previously with PDE5 inhibitors in particular, or PDE inhibitors in general. In particular, vascular conditioning has not been observed in on-demand dosing of a PDE5 inhibitor, or in individuals taking an acute PDE5 inhibitor dose for

a short time span of two to three days. It is expected that vascular conditioning occurs after chronic administration of the PDE5 inhibitor, for example, after about three daily doses of up to 10 mg, preferably after five days of daily dosing, and more preferably after seven days of daily dosing. In addition, after about three days of daily dosing, intermittently missing one chronic dose may lead to a reduction in vascular conditioning, but not a complete loss of conditioning.

It is theorized, but not relied upon herein, that vascular conditioning is caused by a partial or complete reversal of circulatory dysfunctions in penile circulation arising from conditions such as diabetes; atherosclerosis; smoking, hypertension, or a combination of such factors. These conditions result in thickening of the arterial wall, decreased arterial compliance, and decreased responsiveness to endogenous vasodilators, such as nitric oxide.

PDE5 inhibitors vary significantly in chemical structure, and the use of a PDE5 inhibitor as defined in the present invention is not dependent on a particular chemical structure, but rather on the critical parameters outlined herein. However, preferred compounds having the required potency and preferred selectivity can be readily identified by tests described herein from compounds described in Daugan U.S. Patent No. 5,859,006, Daugan et al. U.S. Patent No. 5,981,527, and Daugan et al. U.S. Patent No. 6,001,847, each of which is incorporated herein by reference.

Preferred compounds of Daugan U.S. Patent No. 5,859,006 and Daugan et al. U.S. Patent No. 5,981,527 are represented by structural formula (I):

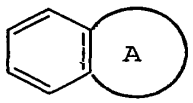


(I)

wherein R^0 is selected from the group consisting of hydrogen, halogen, and C_{1-6}alkyl;

R^1 is selected from the group consisting of 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, aryl-C_{1-3}alkyl, wherein aryl is phenyl or phenyl substituted with one to three substituents selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, methylenedioxy, and mixtures thereof, and heteroarylC_{1-3}alkyl, wherein heteroaryl is thienyl, furyl, or pyridyl, each optionally substituted with one to three substituents selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, and mixtures thereof;

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, saturated or partially or fully unsaturated, and comprises carbon atoms and optionally one or two heteroatoms selected from the group consisting of oxygen, sulphur and nitrogen;

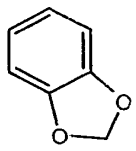
R^3 represents hydrogen or C_{1-3}alkyl, or R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain; and salts and solvates thereof.

Other preferred compounds are those of formula (I) wherein:

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

R^1 is hydrogen or C_{1-6}alkyl;

R^2 is the bicyclic ring



which can be optionally substituted by one or more groups selected from halogen and C_{1-3}alkyl; and

R^3 is hydrogen or C_{1-3}alkyl.

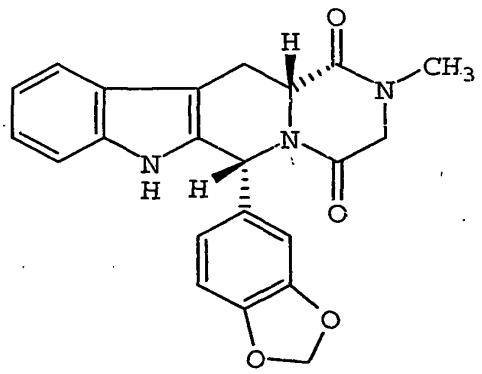
Preferred compounds are:

(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; 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 (e.g., hydrates) thereof.

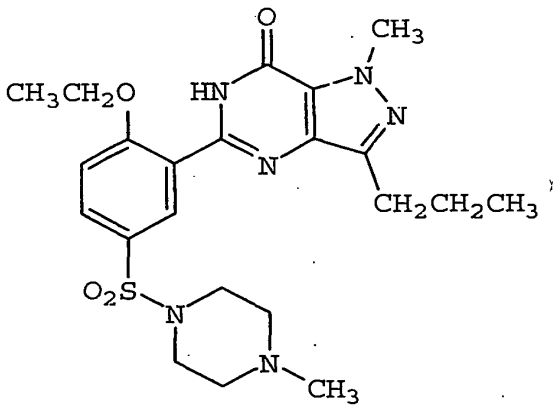
An especially preferred selective PDE5 inhibitor useful in the present invention is (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, alternatively named (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione, which is disclosed in Daugan U.S. Patent No. 5,859,006, and represented by structural formula (II):



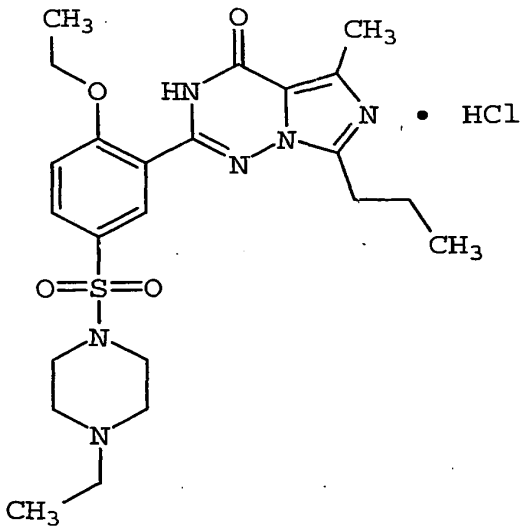
(II)

Other exemplary compounds useful in the present invention are disclosed in Daugan et al. U.S. Patent No. 6,001,847, WO 97/43287, and WO 00/15639, incorporated herein by reference.

In addition, sildenafil and vardenafil can be used as the PDE5 inhibitor for daily dosing.



sildenafil



vardenafil

With respect to sildenafil and vardenafil, the dose for chronic administration is about 1 to about 25 mg/day, and preferably about 1 to about 20 mg/day.

Other useful PDE5 inhibitors that can be used in a chronic dosing regimen of the present invention include, but are not limited to:
5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]-phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl)phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one; and
5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

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 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 serum albumin. PDE5 is present in quantities that yield <30% total hydrolysis of sub-

strate (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 10 µg/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% polyvinylpyrrolidine (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 PDE1c 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} Value 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

The compound of structural formula (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
Hydroxypropylmethylcellulose phthalate	1	5
Microcrystalline Cellulose	221.87	213.87
Croscarmellose Sodium	5.00	5.00
Sodium Lauryl Sulfate	2.50	2.50
Sulfate 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 of structural formula (I).

Example 2

The following formula is used in preparing a finished dosage form containing 10 mg of the compound of structural formula (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 of 5 mg of the compound of structural formula (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 predissolved 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

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

Erectile function was assessed 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. The compound of structural formula (I) significantly improved erectile function as assessed by all endpoints. In both "on demand" and daily dose regimens, the compound of structural formula (I) significantly improved erectile function in doses between 1 and 20 mg.

Example 6

Data from five clinical studies were integrated to show the efficacy of daily dosing of 5 mg and 10 mg of a compound of structural formula (I) (Study Drug). One study was of eight weeks duration, and the other four studies were of twelve weeks duration. The Study Drug was administered "daily" to patients with male erectile dysfunction. "Erectile dysfunction (ED)" is defined as the persistent inability to attain and/or maintain an erection adequate to permit satisfactory sexual performance.

The study population consisted of four subgroups as follows: (a) Study Drug taken less than 30% of the time during the study; (b) Study Drug taken 30% to 50% of the time during the study; (c) Study Drug taken 50% to 70% of the time during the study; and (d) Study Drug taken greater than 70% of the time during the study.

The Study Drug was orally administered as tablets of coprecipitate of Study Drug made in

accordance with Butler U.S. Patent No. 5,985,326 and as tablets containing the Study Drug as a free drug. The Study Drug was administered in 5 mg and 10 mg doses, "daily" and not more than once every 24 hours. No other approved or experimental medications, treatments, or devices used to treat ED were allowed.

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, especially, Question 2 and Question 3. The SEP is a patient diary instrument documenting each sexual encounter during the course of the study.

The safety analysis 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.

Overall, integration of the five studies demonstrated a trend toward better response with increased frequency of dose, both in the 5 mg and 10 mg group, and in all three primary efficacy variables. The results are summarized in following Tables 2-4.

Table 2. Summary of IIEF Erectile Function Domain

		Percent of the time taken drug during the study			
Dose	Statistics	<30%	30% to 50%	50% to 70%	>70%
5mg	N	97	54	28	13
	Mean Baseline	13.2	13.5	14.1	13.1
	Mean Endpoint	17.4	17.5	20.9	22.1
	Mean Change	4.3	4.0	6.8	9.0
10mg	N	164	75	41	43
	Mean Baseline	14.1	14.4	13.9	14.8
	Mean Endpoint	20.0	21.4	21.5	22.2
	Mean Change	5.9	6.9	7.6	7.4

Table 3. Summary of SEP Question 2 (Ability to insert penis)

		Percent of the time taken drug during the study			
Dose	Statistics	<30%	30% to 50%	50% to 70%	>70%
5mg	N	98	54	28	13
	Mean Baseline	42.7	40.8	47.9	42.8
	Mean Endpoint	57.2	57.2	69.3	68.2
	Mean Change	14.4	16.5	21.4	25.5
10mg	N	164	76	41	45
	Mean Baseline	44.7	47.5	43.6	45.9
	Mean Endpoint	66.2	69.0	73.4	75.6
	Mean Change	21.5	21.5	29.9	29.7

Table 4. Summary of SEP Question 3 (Sufficiently long erection for successful intercourse)

		Percent of the time taken drug during the study			
Dose	Statistics	<30%	30% to 50%	50% to 70%	>70%
5mg	N	98	54	28	13
	Mean Baseline	21.8	16.7	18.7	18.4
	Mean Endpoint	38.2	40.4	53.5	54.6
	Mean Change	16.4	23.7	33.8	36.2
10mg	N	164	76	41	45
	Mean Baseline	24.6	26.5	20.2	25.3
	Mean Endpoint	53.5	56.3	63.2	63.9
	Mean Change	28.9	29.7	43.0	38.6

Example 7

A double-blind, placebo-controlled study assessed the safety and efficacy of daily treatment using a compound of formula (I) (Study Drug) in men 21-72 years of age and experiencing mild to moderate erectile dysfunction. Men having a history of radical prostatectomy or diabetes mellitus were excluded. In this study, following a three-week treatment free run-in period, the subjects were randomized to a three week daily treatment with placebo or Study Drug (10, 25, 50, or to 100 mg). All participants in the study agreed to attempt four sexual encounters during both the run-in and treatment periods. Baseline International Index of Erectile Function (IIEF) scores, sexual encounter profile (SEP) diary data, and the global assessment question (GAQ) were collected during the treatment period. Primary endpoints were change from baseline in Questions 3 (treatment effect on penetration ability) and 4 (treatment effect on erection maintenance) of the IIEF. Secondary endpoints

included change from baseline in all IIEF domains and in SEP and GAQ responses. The results for the group administered 10 mg of Study Drug daily were comparable to, or better than, results for groups administered 25, 50, and 100 mg of Study Drug daily.

Compared to the placebo, the Study Drug significantly improved erectile function as assessed by all study endpoints. For example, in groups treated with the Study Drug, the change in IIEF Question 3 was about 1.4 (compared to placebo) with daily 10 mg treatment. The change in Question 4 was about 1.8 (compound to placebo) with 10 mg daily treatment. Successful intercourse rates using the Study Drug, as reported in SEP diaries, were up to 82% with 10 mg daily therapy, compared to 40.4% for placebo. In addition, 90% of the subject receiving 10 mg daily dose of Study Drug reported improved erection on the GAQ compared to 30% of subjects administered a placebo. Adverse events were dose-related, and attenuated with continued daily treatment. The most common adverse events were headache, back pain, myalgia, and dyspepsia. Treatment-related headache, the most common adverse event, was observed in 13% to 46% of subjects receiving daily Study Drug compared to 3% for placebo. There were no treatment-related changes in vital signs, ECG, or laboratory measures.

In accordance with the present invention, a daily unit dose of about 1 to about 10 mg, preferably about 2 to about 10 mg, and most preferably about 5 to about 10 mg, administered daily up to a maximum of 10 mg per day for at least three days,

effectively treats ED, minimizes or eliminates the occurrence of adverse side effects, and improves vascular conditioning. Importantly, the patient is provided spontaneity with respect to sexual activities and a more rapid return to a prearoused state. Surprisingly, in addition to treating ED in individuals, a greater response was observed using a low daily dose compared to a higher on-demand dose of PDE5 inhibitor, in addition to a lower instances of adverse events attributed to lower dose.

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. An article of manufacture for human pharmaceutical use comprising:

(a) an oral dosage form comprising a PDE5 inhibitor having an IC_{50} for the inhibition of PDE5 less than 10 nM, and sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages;

(b) a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by utilizing a chronic dosing regimen; and

(c) a container.

2. An article of manufacture for human pharmaceutical use comprising:

(a) an oral dosage form comprising a PDE5 inhibitor having an IC_{50} less than 10 nM, and a sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages;

(b) a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by utilizing a chronic dosing regimen, wherein the chronic dosing regimen improves vascular conditioning; and

(c) a container.

3. An article of manufacture for human pharmaceutical use comprising:

(a) an oral dosage form comprising of a PDE5 inhibitor having an IC_{50} less than 10 nM, and a sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages;

(b) a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by utilizing a chronic dosing regimen, wherein the chronic dosing regimen improves vascular conditioning compared to an acute or on-demand dosing of sildenafil; and

(c) a container.

4. An article of manufacture for human pharmaceutical use comprising:

(a) an oral dosage form comprising a PDE5 inhibitor having an IC_{50} less than 10 nM, and a sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages;

(b) a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by utilizng a chronic dosing regimen, wherein the chronic dosing regimen improves vascular conditioning compared to an acute or on-demand dosing of vardenafil; and

(c) a container.

5. The article of manufacture of claims 1 through 4, wherein the PDE5 inhibitor further has

(i) at least a 100 fold differential in IC_{50} values for the inhibition of PDE5 versus PDE6, and

(ii) at least 1000 fold differential in IC_{50} values for the inhibition of PDE5 versus PDE1c.

6. The article of claims 1 through 4 wherein the oral dosage form comprises about 1 mg, about 2 mg, about 5 mg, or about 10 mg, of the PDE5 inhibitor.

7. The article of claims 1 through 4 wherein the chronic dosing regimen is a daily dosing regimen.

8. The article of claims 1 through 4 wherein the chronic dosing regimen comprises administration of about 1 mg/day to about 10 mg/day of the PDE5 inhibitor.

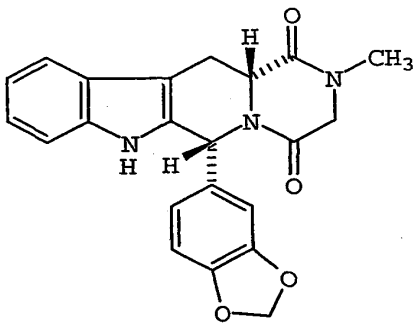
9. The article of claims 1 through 4 wherein the package insert provides a maximum dosage of the PDE5 inhibitor of about 10 mg per day.

10. The article of claims 1 through 4 wherein the PDE5 inhibitor is selected from the group consisting 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;
(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;
5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl]-phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one;
5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsul-phonyl)phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one; and
5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

11. The article of claim 10 wherein the chronic dosing regimen comprises administration of about 1 mg/day to about 10 mg/day of the PDE5 inhibitor.

12. The article of claims 1 through 4 wherein the PDE5 inhibitor is selected from the group consisting of sildenafil and vardenafil.

13. The article of claims 1 through 4, wherein the PDE5 inhibitor has the structure



14. A method of treating sexual dysfunction comprising using an article of manufacture of claims 1 through 4.

15. A method of treating sexual dysfunction comprising a chronic administration to an individual in need thereof of one or more oral dosage form of a PDE5 inhibitor in an amount of about 1 mg/day to about 10 mg/day for at least three days.

16. The method of claim 15 wherein the chronic administration of a PDE5 inhibitor is a daily administration.

17. A method of improving a relaxant response in corpus cavernosum smooth muscle comprising a chronic administration of a PDE5 inhibitor 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 for at least three days.

18. The method of claim 17 comprising the chronic administration of about 1 mg/day to about 25 mg/day of the PDE5 inhibitor.

19. Use of a PDE5 inhibitor 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 vardenafil for the manufacture of a medicament having a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by chronic dosing of about 1 to about 10 mg of the PDE5 inhibitor for at least three days.

20. Use of a PDE5 inhibitor 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 vardenafil for the manufacture of a medicament having a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by chronic dosing of about 1 to about 10 mg of the PDE5 inhibitor for at least three days, and that the treatment is accompanied by improved vascular conditioning.

21. Use of a PDE5 inhibitor 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 vardenafil for the manufacture of a medicament having a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by chronic dosing of about 1 to about 10 mg of the PDE5 inhibitor for at least three days, and improves vascular conditioning compared to a chronic or on-demand dosing of sildenafil.

22. Use of a PDE5 inhibitor 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 for the manufacture of a medicament having a package insert providing that the PDE5 inhibitor is useful to treat sexual dysfunction in a patient in need thereof by chronic dosing of about 1 to about 10 mg of the PDE5 inhibitor for at least three days, and improves vascular conditioning

compared to a chronic or on-demand dosing of vardenafil.

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(81) Designated States *(national)*: 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.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, 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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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6 June 2002

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: DAILY TREATMENT FOR ERECTILE DYSFUNCTION USING A PDE5 INHIBITOR

(57) Abstract: The present invention relates to 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 10 mg unit dosage are useful for the treatment of sexual dysfunction by daily administration of the PDE5 inhibitor. The articles of manufacture described herein are characterized by PDE5 inhibition, and accordingly, provide a benefit in therapeutic areas where inhibition of PDE5 is desired, especially erectile dysfunction, with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes and with an improvement of vascular conditioning.

WO 01/80860 A3

INTERNATIONAL SEARCH REPORT

Inte· tional Application No
PC1/US 01/12512

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/52 A61K31/505 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 A61P

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, WPI Data, PAJ, CHEM ABS Data, EMBASE, SCISEARCH, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 28902 A (PFIZER LTD ;PFIZER (US); PFIZER RES & DEV (IE); ELLIS PETER (GB);) 22 December 1994 (1994-12-22) page 1, line 1-4 page 2, paragraph THIRD page 9 page 6 -page 7; claims 1,5,8 page 10 -page 11	1-11
Y	---	19-22
X	US 6 001 847 A (DAUGAN ALAIN CLAUDE-MARIE ET AL) 14 December 1999 (1999-12-14) column 5, line 39,40 column 6, line 36-53 claims 1,7,13	1-9,13
Y	---	19-22
	-/--	

[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

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"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
19 March 2002	28/03/2002

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	Brunnauer, H

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

INTERNATIONAL SEARCH REPORT

Inter ·ional Application No
PCI/US 01/12512

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 97 03675 A (GLAXO WELLCOME LAB SA ;DAUGAN ALAIN CLAUDE MARIE (FR)) 6 February 1997 (1997-02-06) page 3, line 24,25,30-32 page 4, line 5,6 page 5, line 3-8	1-9
Y	---	19-22
X	T. ROUMEGUÈRE: "Erectiestoornissen: een update over de nieuwe therapeutische mogelijkheden" ACTA UROLOGICA BELGICA, 2000 - 12 April 2000 (2000-04-12), pages 41-42, XP001061828 page 42	1-9,12
Y	-----	19-22

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-9

Present claims 1-9 relate to compounds defined by reference to a desirable characteristic or property, namely "..a PDE5 inhibitor having an IC50 for the inhibition of PDE5 less than 10 nM, and sufficient bioavailability to be effective in about 1 to about 10 mg unit oral dosages..".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds as disclosed in claims 10, 12 and 13 of the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte· *ional Application No
PC1/US 01/12512

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RESPONSE UNDER 37 C.F.R. 116
EXPEDITED PROCEDURE
EXAMINING ART UNIT 1614

PATENT--NO FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

WILLIAM ERNEST PULLMAN ET AL.

Serial No.: 10/031,556

Filed: October 19, 2001

For: **UNIT DOSAGE FORM**

Attorney Docket No. 29342/36206A

Group Art Unit: 1614

Examiner: Rebecca Cook

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Dated: July 21, 2004

James J. Napoli
Registration No. 32,361
Attorney for Applicants

RESPONSE AFTER FINAL UNDER 37 C.F.R. §1.116

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

This is a response to the Office Action of May 21, 2004. Reconsideration and allowance of the application are respectfully requested.

STATUS OF THE CLAIMS

Claims 11-17 and 20-24 currently are pending in the application. All other claims have been cancelled.

All pending claims stand rejected under 35 U.S.C. §103.

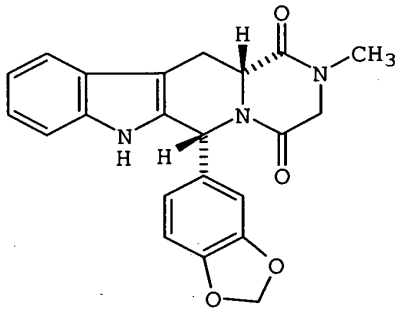
The following more particularly sets forth the current status of the claims:

1.-10. (Cancelled)

11. (Previously amended) The method of claim 13 wherein the sexual dysfunction is male erectile dysfunction.

12. (Previously amended) The method of claim 13 wherein the sexual dysfunction is female arousal disorder.

13. (Previously amended) A method of treating sexual dysfunction in a patient in need thereof comprising orally 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. (Original) The method of claim 13 wherein the unit dose contains about 2 to about 20 mg of the compound.

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

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

17. (Original) 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.-19. (Cancelled)

20. (Previously presented) The method of claim 13 wherein the unit dose contains about 2.5 mg of the compound.

21. (Previously presented) The method of claim 20 wherein the unit dose is administered once per day.

22. (Previously presented) The method of claim 15 wherein the unit dose is administered once per day.

23. (Previously presented) The method of claim 13 wherein the compound is administered as a free drug.

24. (New) The method of claim 13 wherein the unit dose contains about 20 mg of the compound.

RESPONSE UNDER 37 C.F.R. §1.116

This response is submitted in accordance with 37 C.F.R. §1.116(a) and §1.116(b). This response was not presented earlier because applicants believed, and still believe, that the response filed on January 15, 2004, overcame all outstanding issues. The response should be entered because it places the application in better form for allowance or appeal, and the response does not require further searching or present any new issues.

THE FINAL REJECTION IS IMPROPER AND SHOULD BE WITHDRAWN

Applicants respectfully submit that the final rejection is not proper in this case because the examiner has raised a new ground of rejection in addition to the rejection stated on Paper No. 5. The examiner states in this Office Action (FINAL) that there is no showing of similar efficacy comparing 20 mg of the compound of the instant method with the 50 mg disclosed in Daugan U.S. Patent No. 6,140,329. The examiner did not specifically raise this ground of rejection in the previous Office Action, and it is not clear that this ground of rejection is solely based on the currently outstanding rejection under 35 U.S.C. §103. Because the rejection on the above basis is new, applicants have not been given an opportunity to present the arguments to overcome and/or traverse the rejection on this ground. In view of the above, applicants submit that a new ground of rejection has been raised in this Office Action (FINAL), which was not previously stated in the

Paper No. 5. Accordingly, applicants respectfully request that the final rejection be withdrawn.

SUMMARY OF THE INVENTION

The present invention and all pending claims are directed to a method of treating sexual dysfunction in a patient by orally administering a unit dose containing about 1 to about 20 mg of a compound (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) (also referred to as Compound (I)) up to a maximum total dose of 20 mg per day. See, for example, page 5, lines 10-30 of the specification. The sexual dysfunction includes, but is not limited to, male erectile dysfunction (ED) (claim 11) and female arousal disorder (FAD) (claim 12).

ISSUE

Whether claims 11-17 and 20-24 are patentable under 35 U.S.C. §103 over Daugan U.S. Patent No. 6,140,329.

ARGUMENTS

The present invention is not obvious over Daugan et al. (U.S. Patent No. 6,140,329) under 35 U.S.C. §103.

Briefly, U.S. Patent No. 6,140,329 (hereafter '329 patent) discloses a broad range of dosing relating to Compound A and B. Specifically, the '329 patent discloses: "in particular compounds A and B will generally be in the range of from 0.5-800 mg for an aver-

age adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400 mg of active compound." (Column 3 lines 48-55.)

In this case, the '329 patent gives neither an indication of which parameters are critical nor a direction as to which of many possible choices is likely to be successful. See *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). In other words, the '329 patent generally discloses the broad range and nothing more.

Surprising and Unexpected Results of the Present Invention

The present invention as a whole would not have been obvious over '329 patent because the present invention has surprising and unexpected results as discussed below.

An applicant may overcome the rejection under §103 by establishing "that the claimed range is critical" generally by showing that the claimed range achieves results relative to the prior art range. *In re Geisler*, 43 U.S.P.Q.2d 1362, 1365 (Fed. Cir. July 7, 1997). The unit dose range of about 1 to about 20 mg as claimed in claim 13 is critical because this dose range exhibits the surprising and unexpected results of low adverse side effects *and* still being unexpectedly efficacious in treating sexual dysfunction. The present specification discloses the combined clinical studies as illustrated in Table of IIEF (page 31), which shows the efficacy of the compound at a dosing range of 2-100 mg. It is worth noting from this table that the lower doses are found to be efficacious. The

present specification also discloses that doses at a higher level (i.e., above 20 mg), although efficacious, result in an increased level of unpleasant adverse events (see page 32, lines 15-20). The table in Example 7 at page 32 of the specification clearly shows that undesirable adverse side effects, such as headache, dyspepsia, and back pain, are dose related; and an increase in adverse side effects with an increase in unit dose (doses from 25 mg to 100 mg). Also see specification, page 30, lines 15-23 and page 32.

The present specification further discloses "even though efficacy in the treatment of ED was observed at 25 mg to 100 mg unit doses, the adverse events observed from 25 mg to 100 mg dose must be considered," which indicates a dose above 20 mg (or above 25 mg) is not desirable due to an increased level of unwanted adverse side effects; in other words a higher dose above 20 mg would be less tolerable. Accordingly, the present invention teaches that a unit dose of about 1 to about 20 mg, about 2 to about 20 mg, and about 5 to about 20 mg of compound (I) is preferred.

Moreover, it has been recognized by the court that ranges which overlap or lie inside ranges disclosed by the prior art may be patentable if the applicant can show criticality in the claimed range by evidence of unexpected results. *In re Wertheim,* 191 U.S.P.Q. 90, 100 (CCPA 1976); and *In re Geisler*. As stated above, applicants showed the criticality of the claimed range by the evidence of unexpected and surprising results provided by the claimed dose range. This was further corroborated with the Declaration by Dr. Gregory D. Sides filed January 15, 2004. Moreover,

these findings of surprising and unexpected results are commensurate in scope with the claimed range. See *In re Greenfield*, 197 U.S.P.Q. 227, 230 (CCPA 1978) ("Moreover, the applicant's showing of unexpected result must be commensurate in scope with the claimed range.") Additionally, patentability is imparted in this case in view of the '329 patent because the results achieved at the claimed range are unexpected and surprisingly good as discussed above. See *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977).

The examiner stated in the Office Action that the first declaration of Dr. Sides is not persuasive because decreased side effects are expected at lower doses. Applicants respectfully submit that the examiner failed to appreciate the present invention as a whole. In particular, while decreasing a dose of drug often decreases side effects, it also often decreases efficacy. In contrast, the surprising and unexpected results of the present invention include at least two factors: the claimed unit dose range of about 1 to about 20 mg provides substantially decreased adverse side effects while still retaining efficacy. The observed divergence of retained efficacy from decreased side effects in these substantially lower doses is unexpected. It is not predictable that the low dose of about 1 to about 20 mg of Compound (I) would be efficacious. More significantly, it is neither expected from nor suggested by the '329 disclosure that the presently claimed low dose range of about 1 to about 20 mg would be efficacious as well as reduce the adverse events to such level that a patient suffering from erectile dysfunction would be treated effectively. In

other words, the '329 patent does not describe or forecast that a low dosage range of about 1 to about 20 mg would have the effects of efficacy *and* at the same time achieve unexpectedly low adverse side effects.

Therefore, in this case, patentability is imparted because the '329 patent fails to suggest to one of ordinary skilled in the art that the claimed range of the present invention should be carried out and would have likelihood of success. Moreover, the '329 patent disclosure of the broad range of 0.2-400 mg (in tablets or capsules) would not have suggested to one of ordinary skill in the art at the time invention was made that the low dose range of about 1 to about 20 mg would have unexpected surprising results of not only being efficacious but also having low adverse side effects as discussed above.

The examiner also stated in the Office Action that there is no showing of similar efficacy comparing 20 mg of the compound of the instant method with the 50 mg disclosed in the '329 patent. Applicants respectfully submit that the examiner's rejection based on this reason cannot be maintained. As stated above, the present application discloses efficacy data ranging from 2 mg to 100 mg. The examiner has not shown any rational and/or reasonable basis as to why a 20 mg would not be efficacious when the specification clearly discloses that doses below 20 mg and above 20 mg are efficacious (see page 31). One skilled in the art would understand that a 20 mg dose would be efficacious based on the clinical data disclosed in Example 7 of the specification. It is submitted that the examiner is requesting specific data without explaining why that

showing is necessary in this instance. However, in the interest of facilitating prosecution of this application toward a favorable decision, applicants herein file the Second Declaration by Dr. Gregory D. Sides, which shows that the efficacy of a 20 mg dose of Compound (I) is comparable to that of a 50 mg unit dose of Compound (I) in treating ED.

In view of the above, it is submitted that the present claims would not have been obvious over the '329 patent disclosure. Accordingly, applicants respectfully request that the rejection on this ground be withdrawn.

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 LLP

By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
July 21, 2004

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

WILLIAM ERNEST PULLMAN ET AL.

Serial No.: 10/031,556

Filed: October 19, 2001

For: **UNIT DOSAGE FORM**

Attorney Docket No. 29342/36206A

Group Art Unit: 1614

Examiner: Rebecca Cook

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: July 21, 2004

James J. Napoli
Registration No. 32,361
Attorney for Applicants

DECLARATION OF DR. GREGORY D. SIDES, M.D., F.A.C.E.P., F.A.C.P. UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

NOW COMES Dr. Gregory D. Sides, Declarant herein, and states as follows:

1. I presently hold the position of Medical Director, Primary Care Products, Cialis® Product Team at Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285.

2. My previous positions were:

Director, Bioproduct Medical, Eli Lilly and Company, Indianapolis, Indiana (Jan 2002 – Jan 2003)

Director of Operations, Global Clinical Research, Eli Lilly and Company, Indianapolis, Indiana (Feb 2001 – Jan 2002)

Acting Director, Cardiovascular Medical, Eli Lilly and Company, Indianapolis, Indiana (Jul 2000 – Feb 2001)

Senior Clinical Research Physician, Cardiovascular, Medical, Eli Lilly and Company, Indianapolis, Indiana (Jan 1999 - Jul 2000)

Clinical Research Physician, Cardiovascular Division, Eli Lilly and Company, Indianapolis, Indiana (Jul 1994 - Dec 1998)

Clinical Research Physician, Infectious Diseases Division, Eli Lilly and Company, Indianapolis, Indiana (Mar 1990 - Jul 1994)

Associate Clinical Research Physician, Infectious Diseases Division, Eli Lilly and Company, Indianapolis, Indiana (Feb 1988 – Mar 1990)

Partner, Kirtley, Paschall, Sides Emergency Physicians, Inc., Danville, Indiana (Nov 1984 – Mar 1988)

Hendricks Community Hospital, Danville, Indiana (Nov 1984 – Mar 1988)

Emergency Physician, Midwest Medical Management, Inc. Indianapolis, Indiana (Jul 1983 – Nov 1984)

3. I received a degree in Medicine from the Indiana University of Medicine, Indianapolis, Indiana in 1980. I received a B.S. in Chemistry, Magna Cum Laude, from Indiana State University, Terre Haute, Indiana in 1977.

I completed an Internship and Residency in Internal Medicine at Methodist Hospital, Indianapolis, Indiana (1980-1983).

I am board certified in Internal Medicine and Emergency Medicine: Board of Certification: Diplomate, American Board of Internal Medicine, September 14, 1983 (#092096); Diplomate: American Board of Emergency Medicine, March 17, 1989 – December 31, 1999, Recertification, December 24, 1998 – December 31, 2008 (#870725).

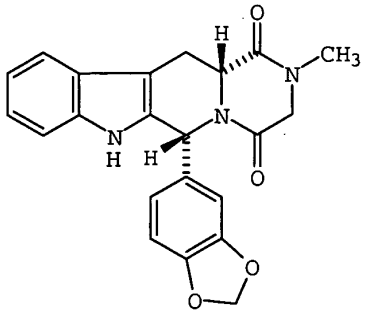
4. I have practiced medicine for twenty three (23) years, conducted research, published about 28 articles, 4 book chapters and 35 abstracts, and presented lectures at numerous conferences, served as a member on numerous editorial boards and scientific or medical advisory boards, and have a membership in numerous societies, such as American Association of Pharmaceutical Physicians, American College of Emergency Physicians, and American College of Physicians.

5. One of my main fields of research and interest is in the field of Internal Medicine, in particular primary care product, cardiovascular, and infectious diseases.

6. I have read and understand U.S. Patent Application Serial No. 10/031,556, and I am familiar with the May 21, 2004 Office Action (Final) in the above-identified application.

7. The invention disclosed in that application is directed to a method of treating sexual dysfunction (Claims 11-17 and 20-23), including, but not limited to, male erectile dysfunction and female sexual arousal disorder, which comprises orally administering to a patient in need thereof one or more unit dose

containing about 1 to about 20 mg of Compound (I) (also refer herein as "tadalafil"), up to a maximum total dose of 20 mg per day.



(I)

8. The present invention is based on detailed experiments and clinical trials, and the unexpected discovery of a unit dosage form incorporating about 1 to about 20 mg of Compound (I) that, when orally administered, effectively treats sexual dysfunction and substantially reduces various undesirable adverse events.

9. The new and surprisingly unexpected results achieved by the present invention are illustrated in Example 7 of the specification in the tables at pages 31 and 32, which show that the lower doses of Compound (I) are not only efficacious but also more tolerable than higher doses (i.e., doses above 20 mg) in treating male erectile dysfunction.

10. Example 7 of the specification in the table at page 31 specifically shows efficacy of Compound (1) at doses ranging from 2 mg to 100 mg evaluated by IIEF. The Table below shows that the efficacy of Compound (I) at 20 mg dose, from an analysis of pooled data from 11 randomized, double-blind, 12-week placebo-controlled trials, is comparable with 50 mg dose (data from Example 7 of the specification).

Table: Efficacy at 20 mg dose and 50 mg dose

	Placebo [1] **(N = 638)**	**Tadalafil** [1] **20 mg (N = 1143)**	**Placebo** [2] **(N = 131)**	**Tadalafil** [2] **50 mg (N = 52)**
Efficacy measure	*Change	*Change	*Change	*Change
IIEF EF domain	0.9	8.6	0.8	9.8

[1] Data from an analysis of pooled data from 11 randomized, double-blind, 12-week placebo-controlled trials
[2] Data from the table of Example 7 of the specification (an analysis of data pooled from three Phase 2 studies)
* Change = change from baseline in the erectile function domain of the International Index of Erectile Function (IIEF): Mean

11. The data in paragraph 10 shows that dose at 20 mg is efficacious in treating erectile dysfunction; the mean IIEF EF domain score increased by 8.6 points for 20 mg tadalafil compared to a less then 1 point in the placebo group (0.9). Similarly, the mean IIEF EF domain score increased by 9.8 compared to a less than 1 point in the placebo group (0.8) for 50 mg dose as shown above. Therefore, the efficacy of 20 mg dose is comparable to the efficacy of 50 mg dose.

12. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or document or any patent resulting therefrom.

Gregory D. Sides, M.D.

Date: 14 Jul 2004, 2004

BEST AVAILABLE COPY

PATENT APPLICATION FEE DETERMINATION RECORD
Effective O[illegible]er 1, 2001

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				☐

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

7/26/4

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 12	Minus	** 46	= 0
Independent	* 1	Minus	*** 3	= 0
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

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.

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BOX AF

IFW
AF

RESPONSE UNDER 37 C.F.R. 116
EXPEDITED PROCEDURE
EXAMINING ART UNIT 1614

PATENT--NO FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
WILLIAM ERNEST PULLMAN ET AL.	
Serial No.: 10/031,556	
Filed: October 19, 2001	
For: **UNIT DOSAGE FORM**	
Attorney Docket No. 29342/36206A	Dated: July 21, 2004
Group Art Unit: 1614	
Examiner: Rebecca Cook	James J. Napoli Registration No. 32,361 Attorney for Applicants

RESPONSE AFTER FINAL UNDER 37 C.F.R. §1.116

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

All to enter
RC 11/16/04

This is a response to the Office Action of May 21, 2004. Reconsideration and allowance of the application are respectfully requested.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

4743 7590 09/01/2004

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
COOK, REBECCA	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 09/01/2004

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

Advisory Action	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 July 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: *none*.

   Claim(s) rejected: *11-17 and 20-24*.

   Claim(s) withdrawn from consideration: *none*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Rebecca Cook
REBECCA COOK
PRIMARY EXAMINER
GROUP 1200/1614

Continuation of 5. does NOT place the application in condition for allowance because: Applicants' argument that final rejection should be withdrawn is not persuasive, since the statement regarding comparing the efficacy of the instant 20 mg of the compound of the instant mehtod with the 50 mg disclosed in Daugan is in response to the Declaration under 37 CFR 1.132 submitted on January 15, 2004. The Declaration under 37 CFR 1.132 of July 26, 2004 is not persuasive, since no unexpected results is seen comparing the instant 20 mg with the 50 mg of Daugan when the standard deviation data are considered. Furthermore, the Declaration of July 25, 2004 does not include SD data or the P value.

Fractile Function Domain Change from Baseline

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NOTICE OF ALLOWANCE AND FEE(S) DUE

04743 7590 11/17/2004

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
COOK, REBECCA	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/17/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

TITLE OF INVENTION: COMPOSITIONS COMPRISING PHOSPHODIESTERASE INHABITORS FOR THE TREATMENT OF SEXUAL DISFUNCTION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1370	$0	$1370	02/17/2005

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 11/04) Approved for use through 04/30/2007.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

04743 7590 11/17/2004

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (703) 746-4000, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

TITLE OF INVENTION: COMPOSITIONS COMPRISING PHOSPHODIESTERASE INHABITORS FOR THE TREATMENT OF SEXUAL DISFUNCTION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1370	$0	$1370	02/17/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
COOK, REBECCA	1614	514-250000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

04743 7590 11/17/2004

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
COOK, REBECCA	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/17/2004

Determination of Patent Term Extension under 35 U.S.C. 154 (b)
(application filed after June 7, 1995 but prior to May 29, 2000)

The Patent Term Extension is 0 day(s). Any patent to issue from the above-identified application will include an indication of the 0 day extension on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Extension is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 11/04) Approved for use through 04/30/2007.

Notice of Allowability	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *interview of November 10, 2004*.

2. ☒ The allowed claim(s) is/are *13, 11-12, 14-17, 20-24, now 1-12*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *11/10/04* .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

11/16/2004 LHOTTIE1 00000001 132855 10031556
01 FC:1253 980.00 DA

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

No statistical difference seen in the change from the baseline for the placebo at 20 mg of tadalafil and 50 mg of tadalafil, which is respectively .9 vs. .8. No statistical difference seen in the change in efficacy between 20 mg and 50 mg, which is 8.6 vs. 9.8, respectively. However, the adverse side effects at 20 mg are dramatically reduced when compared to 50 mg. This data has been set forth in the showings submitted on July 26, 2004 and January 15, 2004. This demonstrates unexpected results of the 20 mg dose of tadalafil over the 50 mg dose.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Extension of Time

The Director may charge Deposit Account No. 13-2855 for any fees for extension of time that might be required. Any extension of time under 37 CFR 1.136(a) that may be required has been authorized by Mr. Napoli.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Cook whose telephone number is (571) 272-0571. The examiner can normally be reached on Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Renee Jones (571) 272-0547 in Customer Service.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The official fax number is 703-872-9806

Rebecca Cook

Primary Examiner
Art Unit 1614

November 10, 2004

Interview Summary	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Rebecca Cook*.

(2) *James Napoli*.

(3) *Soon Hee Jang*.

(4) _____.

Date of Interview: *10 November 2004*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *claims pending*.

Identification of prior art discussed: *art of record*.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *see attached page*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Ms Jang reviewed the results of the two showings. The change from the baseline for the placebo at both 20 mg of tadalafil and 50 mg of tadalafil is respectively .9 vs. .8, which is virtually the same. The change from baseline for tadalafil at 20 mg compared to the change for 50 mg of tadalafil is 8.6 vs. 9.8. There is no statistically difference seen in the change in efficacy between 20 mg and 50 mg. Furthermore, the adverse side effects at 20 mg are dramatically reduced when compared to 50 mg. This demonstrates unexpected results of the 20 mg dose of tadalafil over the 50 mg dose.

Mr. Napoli authorized the Office to charge deposit account 13-2855 for any fees for extension of time that might be required.

Issue Classification	Application No.	Applicant(s)	
	10/031,556	PULLMAN ET AL.	
	Examiner	Art Unit	
	Rebecca Cook	1614	

ISSUE CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)	
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)
514	250		

INTERNATIONAL CLASSIFICATION						
A	61	K	31/495			
A	61	K	31/50			
			/			
			/			
			/			

(Assistant Examiner) (Date)

Patterson 11/15/04
(Legal Instruments Examiner) (Date)

REBECCA COOK
PRIMARY EXAMINER
GROUP 1200
1614
Primary Examiner (Date) 11/10/04

Total Claims Allowed:

O.G. Print Claim(s)	O.G. Print Fig.
1	0

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
	4		34		64		94		124		154		184
	5		35		65		95		125		155		185
	6		36		66		96		126		156		186
	7		37		67		97		127		157		187
	8		38		68		98		128		158		188
	9		39		69		99		129		159		189
	10		40		70		100		130		160		190
2	11		41		71		101		131		161		191
3	12		42		72		102		132		162		192
1	13		43		73		103		133		163		193
4	14		44		74		104		134		164		194
5	15		45		75		105		135		165		195
6	16		46		76		106		136		166		196
7	17		47		77		107		137		167		197
	18		48		78		108		138		168		198
	19		49		79		109		139		169		199
8	20		50		80		110		140		170		200
9	21		51		81		111		141		171		201
10	22		52		82		112		142		172		202
11	23		53		83		113		143		173		203
12	24		54		84		114		144		174		204
	25		55		85		115		145		175		205
	26		56		86		116		146		176		206
	27		57		87		117		147		177		207
	28		58		88		118		148		178		208
	29		59		89		119		149		179		209
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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	8/22/06
	2	7/10/07
	3	9/16/07
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If more than 150 claims or 9 actions staple additional sheet here

BEST AVAILABLE COPY

SEARCH

Class	Sub.	Date	Exmr.
514	250	8/28/02	[illegible]
updated		4/9/03	[illegible]
updated		9/16/03	[illegible]
updated		5/17/04	[illegible]
updated		11/10/04	[illegible]

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
514	250	11/10/04	[illegible]

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

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

IFW

B

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:

WILLIAM ERNEST PULLMAN ET AL.

Serial No.: 10/031,556

Filed: October 19, 2001

For: **UNIT DOSAGE FORM**

Attorney Docket No. 29342/36206A

Group Art Unit: 1614

Examiner: Rebecca Cook

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dated: November 22, 2004

James J. Napoli
Registration No. 32,361
Attorney for Applicants

INTERVIEW SUMMARY

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

The courteous interview granted to applicants' undersigned attorney and Soonhee Jang by Examiner Cook on November 10, 2004 is hereby acknowledged with appreciation. During the interview, the Advisory Action and the January 15 and July 25, 2004 Declarations of Dr. Gregory D. Sides were discussed.

An agreement was reached and Examiner Cook stated that a Notice of Allowance would be issued.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
November 22, 2004

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

04743 7590 11/17/2004

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

12/10/2004 WASFAW2 00000034 10031556

01 FC:1501 1370.00 OP
02 FC:8001 12.00 OP

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Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (703) 746-4000, on the date indicated below.

James J. Napoli	(Depositor's name)
James J. Napoli	(Signature)
December 6, 2004	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

TITLE OF INVENTION: COMPOSITIONS COMPRISING PHOSPHODIESTERASE INHABITORS FOR THE TREATMENT OF SEXUAL DISFUNCTION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1370	$0	$1370	02/17/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
COOK, REBECCA	1614	514-250000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Marshall,
2 Gerstein &
3 Borun LLP

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: LILLY ICOS LLC.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Wilmington, Delaware

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:
☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☒ Advance Order - # of Copies 4

4b. Payment of Fee(s):
☒ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 13-2855 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature James J. Napoli Date December 6, 2004

Typed or printed name James J. Napoli Registration No. 32,361

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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PRINTER RUSH
(PTO ASSISTANCE)

Application :	10/031,556	**Examiner :**	Cook	**GAU :**	1614
From:	CA	**Location:**	(IDC) FMF FDC	**Date:**	1/13/05

Tracking #: 6045012 Week Date: 11-29-04

DOC CODE	DOC DATE	MISCELLANEOUS
☒ 1449	5-24-04	☐ Continuing Data
☐ IDS		☐ Foreign Priority
☐ CLM		☐ Document Legibility
☐ IIFW		☐ Fees
☐ SRFW		☐ Other
☐ DRW		
☐ OATH		
☐ 312		
☐ SPEC		

[RUSH] **MESSAGE:** Please initial / line through Citation dated 5/24/04. Copy provided for reference.

Thank You

CA

[XRUSH] **RESPONSE:**

INITIALS:

NOTE: This form will be included as part of the official USPTO record, with the Response document coded as XRUSH.

REV 10/04

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,556	10/19/2001	William Ernest Pullman	29342/36206A	6526

4743 7590 03/02/2005

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
COOK, REBECCA	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/02/2005

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

PTO-90C (Rev. 10/03)

Notice of Allowability	Application No. 10/031,556	Applicant(s) PULLMAN ET AL.	
	Examiner Rebecca Cook	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.

2. ☐ The allowed claim(s) is/are _____.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 5/24/04
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____

REBECCA COOK
PRIMARY EXAMINER
GROUP 1200-1614

Form 1449PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/031,556
Filing Date	October 19, 2001
First Named Inventor	William Ernest Pullman
Group Art Unit	1614
Examiner Name	Rebecca Cook
Attorney Docket Number	29342/36206A

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number	Publication Date MM-DD-YYYY

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document	Publication Date MM-DD-YYYY
RN		WO 99 59584	11/25/1999
RN		WO 00 53148	09/14/2000
RN		WO 00 66114	11/09/2000
RN		WO 01 80860	11/01/2001

OTHER PRIOR ART – NONPATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published.

Examiner Signature	RCook	Date Considered	2/3/05

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

PRINTER RUSH
(PTO ASSISTANCE)

Application :	10/031556	**Examiner :**	Cook	**GAU :**	1614
From:	CA	**Location:**	(IDC) FMF FDC	**Date:**	1/13/05

Tracking #: 0045012 Week Date: 11-29-04

DOC CODE	DOC DATE	MISCELLANEOUS
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☐ DRW		
☐ OATH		
☐ 312		
☐ SPEC		

[RUSH] **MESSAGE:** Please initial / Tue through Citation dated 5/24/04. Copy provided for reference.

Thank You

CA

[XRUSH] **RESPONSE:** Signed

INITIALS: MC

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REV 10/04

PATENT--FEE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to:
WILLIAM E. PULLMAN ET AL.	
Patent No. 6,943,166	
Issued: September 13, 2005	
Serial No. 10/031,556	Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450.
Filed: October 19, 2001	
For: **COMPOSITIONS COMPRISING PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF SEXUAL DYSFUNCTION**	Dated: May 16, 2006
Attorney Docket No. 29342/36206A	James J. Napoli Registration No. 32,361 Attorney for Applicants

REQUEST FOR CERTIFICATE OF CORRECTION UNDER RULES 322(a) & 323

05/22/2006 BABRAHA1 00000013 6943166
01 FC:1811 100.00 OP

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Patentees respectfully request a Certificate of Correction to be issued for the above-identified U.S. Patent correcting the patent as noted in the attached "Certificate of Correction" form PTO 1050. Duplicate copies of the form are attached hereto.

Errors in the patent can be verified by reference to the application as follows:

Certificate
MAY 24 2006
of Correction

MAY 24 2006

Appln. Page #	Appln. Line #	Column #	Line #	Error by
Notice of Allowance		First Page	54	PTO
Notice of Allowance		1	1-4	PTO
2	2	1	35	PTO
2	2,3	1	35	PTO
2	6	1	38	PTO
2	20	1	51	PTO
2	last line	1	62	applicants
3	22	2	14	PTO
4	15	2	36	PTO
4	24	2	44	PTO
7	1	3	45	PTO
9	14	4	45	PTO
11	30	5	53-54	PTO
12	29-30	6	15	PTO
12	32	6	17	PTO
12	34	6	19	PTO
13	24	6	41	PTO
14	6	6	53	PTO
14	14	6	61	PTO
17	10-11	8	7	PTO
18	26	8	48	PTO
21	2	9	43-44	PTO
26	26	12	11	PTO

Our check in the amount of $100.00 to correct the error(s) by patentee(s) is submitted herewith.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
May 16, 2006

PTO/SB/44 (02-01)
Approved for use through 01/31/2004. OMB 0651-0033
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,943,166

DATED : 09/13/2005

INVENTOR(S) : **PULLMAN ET AL.**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

First page, line 54, in the title, "INHABITORS" should be --INHIBITORS-- and "DISFUNCTION" should be --DYSFUNCTION--

Column 1, lines 1-4, in the title, "INHABITORS" should be --INHIBITORS-- and "DISFUNCTION" should be --DYSFUNCTION--

Column 1, line 35, "CGMP" should be -- cGMP --

Column 1, line 35, delete "lyzing"

Column 1, line 38, "PDES" should be -- PDE5 --

Column 1, line 51, "3 rM" should be -- 3 nM --

Column 1 line 62, "vison" should be -- vision --

Column 2, line 14, "PDES" should be -- PDE5 --

MAILING ADDRESS OF SENDER:
James J. Napoli, Ph.D.
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357

PATENT NO.: 6,943,166

No. of additional copies: 1

MAY 24 2006

PTO/SB/44 (02-01)
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Column 4, line 45, "Iarts." should be -- arts. --

Column 5, lines 53-54, "VIAGRA" should be -- VIAGRA® --

Column 6, line 15, "2xSC-leu" should be -- 2X SC-leu --

Column 6, line 17, "2xYEP/" should be -- 2X YEP/ --

Column 6, line 19, "-700C." should be -- -70°C. --

Column 6, line 41, "ZnSO,)." should be -- $ZnSO_4$). --

Column 6, line 53, "[^{32}p]cGMP to [32p]5'GMP" should be -- [^{32}P]cGMP to [^{32}P]5'GMP --

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Column 6, line 61, "MgCl," should be -- $MgCl_2$, --

Column 8, line 7, "polyvinylpurrolidine" should be -- polyvinylpyrrolidine --

Column 8, line 48, "ICS,," should be -- IC_{50}, --

Column 9, lines 43-44, "scintillatio n" should be -- scintillation --

Column 12, line 11, "PDES" should be -- PDE5 --

MAILING ADDRESS OF SENDER:
James J. Napoli, Ph.D.
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357

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Chicago, Illinois 60606-6357

PATENT NO.: 6,943,166

No. of additional copies: 1

MAY 24 2006

SPE RESPONSE FOR CERTIFICATE OF CORRECTION

Paper No.: _____

DATE : June 2, 2006

TO SPE OF : ART UNIT 3724

SUBJECT : Request for Certificate of Correction for Appl. No.: 10/031556 Patent No.: 7,024,776 B2

Please respond to this request for a certificate of correction within 7 days.

Please review the requested changes/corrections as shown in the **COCIN** document(s) in the IFW application image. No new matter should be introduced, nor should the scope or meaning of the claims be changed.

Please complete the response (see below) and forward the completed response to scanning using document code **COCX**.

Magdalene Talley

Certificates of Correction Branch

703-308-9390 ext. 116

Thank You For Your Assistance

The request for issuing the above-identified correction(s) is hereby:

Note your decision on the appropriate box.

- ☐ **Approved** — **All** changes apply.
- ☐ **Approved in Part** — Specify below which changes **do not** apply.
- ☐ **Denied** — State the reasons for denial below.

Comments: _____

_____

_____

_____

_____

_____ _____

SPE **Art Unit**

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,943,166 B1
APPLICATION NO. : 10/031556
DATED : September 13, 2005
INVENTOR(S) : Pullman et al.

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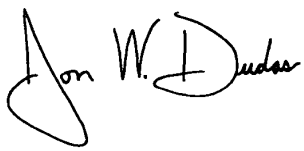
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 6, line 53, "[^{32}p] cGMP to [32p]5'GMP" should be -- [^{32}P] cGMP to [^{32}p] 5'GMP --

Signed and Sealed this

Eighth Day of August, 2006



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Paper 13
Entered: September 1, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTELGENX CORPORATION,
Petitioner,

v.

ICOS CORPORATION,
Patent Owner.

Case IPR2016-00678
Patent 6,943,166 B1

Before SHERIDAN K. SNEDDEN, SUSAN L. C. MITCHELL, and ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

INTRODUCTION

IntelGenX Corporation ("Petitioner") filed a Petition (Paper 1, "Pet.") to institute an *inter partes* review of claims 1–12 of U.S. Patent No. 6,943,166 B1 (Ex. 1001, "the '166 patent"). ICOS Corporation ("Patent Owner") timely filed a Preliminary Response. Paper 11 ("Prelim. Resp.").

Based on this record, we determine Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. *See* 35 U.S.C. § 314(a). Therefore, we deny institution of an *inter partes* review.

Related Proceedings

According to the parties, there are no related matters that would affect or be affected by this proceeding. Pet. 59; Paper 8, 2.

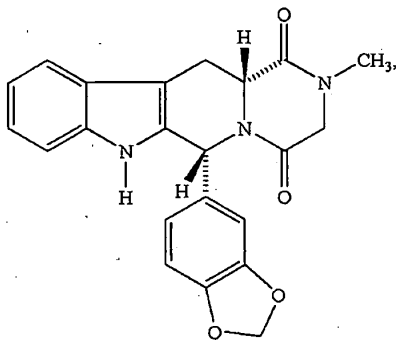
The '166 Patent

The '166 patent relates to a highly selective phosphodiesterase (PDE) enzyme inhibitor and its use in a pharmaceutical unit dosage form. Ex. 1001, Abstract, 1:14–16.

Type 5 cGMP-specific PDE (PDE5) is an attractive target in the treatment of sexual dysfunction. *Id.* at 1:34–39. Before the '166 patent invention, a pharmaceutical product, which provides a PDE5 inhibitor, was available and marketed for treating male erectile dysfunction ("ED") under the trademark VIAGRA®. *Id.* at 1:41–43. The active ingredient in VIAGRA® is sildenafil. *Id.* at 1:43–44. According to the '166 patent, however, "[w]hile sildenafil has obtained significant commercial success, it has fallen short due to its significant adverse side effects." *Id.* at 1:58–60.

The '166 patent discloses a pharmaceutical unit dosage composition comprising about 1 to about 20 mg of compound tadalafil, which has the

following structure:



Id. at 3:11–28. The '166 patent discloses that the pharmaceutical unit dosage is suitable for oral administration, and is useful for treating sexual dysfunction. *Id.* at 3:29–31.

Illustrative Claim

Claim 1 is the sole independent claim challenged in the Petition. It reads:

1. A method of treating sexual dysfunction in a patient in need thereof comprising orally 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 [of formula (I)].

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds, each of which challenges the patentability of claims 1–12:

Basis	References
§ 103	Daugan[1]
§ 103	Daugan and SNDA[2]

[1] Daugan, WO 97/03675, published Feb. 6, 1997 (Ex. 1002, "Daugan").

[2] Center for Drug Evaluation and Research, Approval Package for VIAGRA®, Approval Date March 27, 1998 (Ex. 1003, "SNDA").

In support of its patentability challenges, Petitioner relies on the Declaration of Drs. Wayne J.G. Hellstrom (Ex. 1005) and Douglas Reid Patterson (Ex. 1007).

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to construe any term expressly.

Prior Art Disclosures

Daugan

Daugan identifies (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxyphenyl)pyrazino[2',1':6.1] pyrido[3,4-b]indole-1,4-dione, also known as compound (A), as a compound of the invention. Ex. 1002, 3:24–25. Compound (A) is the same as the compound of formula (I) in the '166 patent, i.e., tadalafil.

Daugan teaches that tadalafil is useful for treating male or female

sexual dysfunction. *Id.* at 4:25–28. According to Daugan, tadalafil may be administered orally to treat erectile dysfunction. *Id.* at 3:30–32. It also teaches that "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." *Id.* at 5:4–7. Specifically, Daugan teaches preparing tablets with 50 mg active compound. *Id.* at 12:15–14:16.

SNDA

SNDA teaches sildenafil is a potent PDE5 inhibitor and is useful for treating ED. Ex. 1003, 35. Sildenafil is therapeutically effective for treating ED at doses of 25, 50, and 100 mg. *Id.* at 127–28, 215, 217–19. According to SNDA, in some patients, doses as low as 5 and 10 mg are therapeutically effective over placebo. *Id.* SNDA states that the "maximum recommended dosing frequency is once per day." *Id.* at 50.

Obviousness Grounds

Petitioner contends that claims 1–12 would have been obvious over the teachings of Daugan, either alone or in combination with SNDA. Pet. 20–46. In both obviousness grounds, Petitioner relies on both Daugan and SNDA for suggesting tadalafil dose recited in claim 1. Based on the current record, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

Specifically, Petitioner points to Daugan for teaching tadalafil formulations comprising individual tablets or capsules containing "from 0.2-400mg of active compound." *Id.* at 22, 25 (citing Ex. 1002, 5). According to Petitioner, while Daugan provides examples of 50 mg dosage forms for oral administration, it teaches that "other strengths" and "other doses" may

be prepared, and that "lower dose ranges may be merited." *Id.* at 23, 25 (citing Ex. 1002, 12–16). In addition, Petitioner refers to SNDA for teaching that sildenafil is therapeutically effective in treating ED at doses of 25, 50, and 100 mg. *Id.* at 39 (citing Ex. 1003, 127–28, 215, 217–19). In some patients, Petitioner asserts, sildenafil is therapeutically effective in dosages as low as 5 to 10 mg. *Id.* at 26, 39 (citing Ex. 1003, 127–28, 215, 217–19).

According to Petitioner, because tadalafil is a more potent and highly selective PDE5 inhibitor, an ordinary artisan would have had a reason to use doses lower than the 50 mg dose exemplified in Daugan, including doses lower than the known effective doses of sildenafil, and would have had a reasonable expectation of success in doing so. *Id.* at 26–28, 42–44. As a result, Petitioner contends, one of ordinary skill in the art would have arrived at the method of claim 1 either by following the express teachings and guidance in Daugan, or through routine optimization. *Id.* at 29, 44.

In its Preliminary Response, Patent Owner does not address the "unit dose containing about 1 to about 20 mg" limitation. Patent Owner, instead, emphasizes that Petitioner fails to account for another essential claim limitation—"a maximum total dose of 20 mg per day." Prelim. Resp. 13–22. We agree with Patent Owner.

In an *inter partes* review, the petition must specify where each element of the claim is found in the prior art. 37 C.F.R. § 42.104(b)(4). Claim 1 recites "orally administering one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day." In general, all patent claim terms are presumed to have meaning. *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006). Petitioner, however,

paraphrases the claim as "recit[ing] a method of treating sexual dysfunction comprising administering a tadalafil dose range of 'about 1 to about 20 mg.'" Pet. 21. In other words, Petitioner appears to ignore the maximum-total-dose requirement. Petitioner's analysis reflects this omission. Assuming, without deciding, that tadalafil would have been expected to be therapeutically effective at doses from "about 1 to about 20 mg," Petitioner does not point to the asserted prior art or otherwise explain why an ordinary artisan would limit the tadalafil dose to 20 mg per day.

As a result, based on the current record, we conclude Petitioner has not established a reasonable likelihood it would prevail in showing that claim 1 would have been obvious over Daugan, either alone or in combination with SNDA.

CONCLUSION

On this record, Petitioner has not demonstrated a reasonable likelihood of prevailing on its challenges to the patentability of any challenged claim of the '166 patent on the grounds asserted in the Petition.

ORDER

Accordingly, it is

ORDERED that Petitioner's request for an *inter partes* review of claims 1–12 of the '166 patent is *denied* and no *inter partes* review is instituted.

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AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Eastern District of Virginia on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:16cv1120	9/2/2016	Eastern District of Virginia

PLAINTIFF	DEFENDANT
Eli Lilly and Company, et al.	Alembic Pharmarceuticals Ltd., et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,943,166	9/13/2005	Lily ICOS LLC.
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Fernando Galindo		

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Eastern District Virginia - Alexandria on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:16-cv-1122	9/2/2016	Eastern District Virginia - Alexandria

PLAINTIFF	DEFENDANT
Eli Lilly and Company, et al.	Mylan Pharmaceuticals Inc.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,943,166	9/13/2005	Eli Lilly and Company
2			
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Eastern District - Virginia on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:16-cv-1208	9/22/2016	Eastern District - Virginia

PLAINTIFF	DEFENDANT
Eli Lilly and Company, et al.	Cipla Limited, et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,943,166	9/13/2005	Lilly ICOS, LLC
2			
3			
4			
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**