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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

METUCHEN PHARMACEUTICALS, LLC

Plaintiff,

vs.

EMPOWER PHARMACEUTICALS LLC
EMPOWER CLINIC SERVICES LLC
SHAUN NOORIAN and
ARTA S. NOORIAN

Defendants

Civil Action No._____

Hon._____

**COMPLAINT**

This is a civil Complaint for patent infringement. Plaintiff, METUCHEN PHARMACEUTICALS LLC of Cranford NJ ("Metuchen"), states as follows:

**JURISDICTION AND VENUE**

1. Metuchen Pharmaceuticals LLC is a limited liability company organized and existing under the laws of the State of New Jersey. Metuchen has its principal place of business at 11 Commerce Drive, 1st floor, Cranford NJ 07016.

2. Defendant Empower Pharmaceuticals LLC is a limited liability company organized and existing under the laws of the State of Texas, with its

principal place of business at 5980 West Sam Houston Parkway North, Suite 300, Houston TX 77041.

3. Defendant Shaun Noorian lists himself as the sole owner of, the sole member of and the Registered Agent for Empower Pharmaceuticals LLC.

4. Empower Clinic Services LLC is a limited liability company organized and existing under the laws of the State of Texas, with its principal place of business at the same location as Empower Pharmaceuticals LLC. Empower Clinic Services does business under the alias "Empower Pharmacy."

5. Defendant Arta S. Noorian lists himself as the sole owner and sole member of Empower Clinic Services LLC. Defendant Arta S. Noorian lists Shaun Noorian as the registered agent for Empower Clinic Services LLC.

6. Empower Pharmaceuticals LLC and Empower Clinic Services LLC a/k/a Empower Pharmacy share the same office. They are thus here referred to collectively as "Empower."

7. This Court has original jurisdiction over this matter pursuant to 28 U.S.C. § 1332(a) because this is a complaint for patent infringement.

8. Venue is proper in this Court pursuant to 28 U.S.C. § 1391(a) and (c).

**FACTUAL BACKGROUND**

9. Plaintiff Metuchen Pharmaceuticals markets STENDRA® avanafil in The United States of America.

10. United States letters patent no. 6656935 (**Exhibit A**) claims avanafil. *See e.g.*, claim 1. The United States Food & Drug Administration accordingly provides public notice that avanafil is covered by the '935 patent. *See* **Exhibit B**.

11. Metuchen Pharmaceuticals is the exclusive licensee of the '935 patent.

12. Empower sells its products throughout the U.S.A. *See* **Exhibit C**. These products include avanafil "orally disintegrating tablets" and "troches." *See* **Exhibit D**. Empower's manufacture, use, offer to sell, and sale of avanafil tablets/troches infringes the '935 patent. *See* 35 U.S.C. § 271(a).

13. On information and belief, Empower does not make the avanafil active ingredient it uses in its tablets/troches. Rather, Empower purchases potentially-contaminated active ingredient from abroad and illicitly imports it into The United States. The United States Food & Drug Administration has not approved that potentially-contaminated active ingredient for sale in the U.S.A. Empower thus imports this potentially-contaminated it into the U.S.A. behind

FDA's back. Empower's importation of avanafil active ingredient infringes the '935 patent. *See* 35 U.S.C. § 271(a).[1]

14. On June 1, 2018 Plaintiff delivered to Defendants a cease-and-desist request. *See* **Exhibit E**. Defendants refuse to respond.

15. Defendants' knock-off avanafil infringes the '935 patent. Defendants' knock-off product may contain contaminated active ingredient and endanger patient safety. Defendants' refusal to even respond to Plaintiff betrays a cavalier indifference to third-party property rights and patient safety.

16. This would be quite troubling were it a stand-alone instance. Unfortunately, it is not. Rather, it is part of a pattern of behavior. For example, Vivus Inc. (not a party to this proceeding) markets QSYMIA®. QSYMIA®, like avanafil, is patented. The FDA provides public notice of this. **Exhibit F**. QSYMIA® is also a suspected teratogen. The FDA thus forbids its sale unless the patient is enrolled in an FDA-approved program to assure the patient does not get pregnant while taking QSYMIA®. Defendants, ignoring both the patents and the teratogen risk, marketed knock-off QSYMIA® *without even bothering to enroll the patients in the legally-required FDA-approved patient-protection program*. *See* **Exhibit G**. Defendants thus, in their rush to make a quick buck,

[1] Defendants' importation of an unapproved, potentially-contaminated new drug with the intent to market also appears at first glance to be a criminal violation of the Federal Food, Drug & Cosmetic Act.

both infringed the QSYMIA® patents and exposed unborn fetuses to the risk of incurring birth defects.

17. The Defendants willfully and repeatedly disregard patent rights and endanger patients. Plaintiff accordingly names Shaun Noorian and Arta S. Noorian - respectively, the sole owners of Empower Pharmaceuticals LLC and Empower Clinic Services LLC - as defendants in their personal capacity.

## FIRST COUNT

**(Patent Infringement)**

18. Metuchen repeats the foregoing allegations as if set forth herein at length.

19. Defendants' importation of and/or manufacture of avanafil infringes the '935 patent. Defendants' offering for sale and/or sale of avanafil-containing products infringes the '935 patent.

20. Defendants' infringement is willful.

**WHEREFORE,** Metuchen respectfully asks the Court to issue an Order in substance equivalent to the attached **Exhibit H**, and for such other relief as the court deems just.

**PHARMACEUTICAL PATENT ATTORNEYS, LLC**
Attorneys for Plaintiff

By ___/mark pohl/_____
J. Mark Pohl, Esq.

Dated: July 5, 2018

## CERTIFICATION

I hereby certify that the matter in controversy is not the subject of any other court, arbitration or administrative proceeding.

__/mark pohl/_____
J. Mark Pohl, Esq.

EXHIBIT A

United States letters patent no. 6656935

US006656935B2

(12) **United States Patent**
**Yamada et al.**

(10) **Patent No.: US 6,656,935 B2**
(45) **Date of Patent: Dec. 2, 2003**

(54) **AROMATIC NITROGEN-CONTAINING 6-MEMBERED CYCLIC COMPOUNDS**

(75) Inventors: **Koichiro Yamada**, Saitama-ken (JP); **Kenji Matsuki**, Saitama-ken (JP); **Kenji Omori**, Saitama (JP); **Kohei Kikkawa**, Kawaguchi (JP)

(73) Assignee: **Tanabe Seiyaku Co., Ltd.**, Osaka (JP)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/925,892**

(22) Filed: **Aug. 10, 2001**

(65) **Prior Publication Data**

US 2003/0032647 A1 Feb. 13, 2003

**Related U.S. Application Data**

(63) Continuation of application No. PCT/JP00/06258, filed on Sep. 13, 2000.

(30) **Foreign Application Priority Data**

Sep. 16, 1999 (JP) ..... 11-261852
Apr. 28, 2000 (JP) ..... 2000-130371

(51) **Int. Cl.**[7] ..... **C07D 239/48**; C07D 403/04; C07D 401/04; A61K 31/506; A61P 15/10

(52) **U.S. Cl.** ..... **514/230.5**; 514/231.5; 514/252.01; 514/275; 544/323; 544/325; 544/105; 544/114; 544/238

(58) **Field of Search** ..... 544/323, 325, 544/105, 114, 238; 514/275, 230.5, 231.5, 252.01

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*Primary Examiner*—Richard L. Raymond
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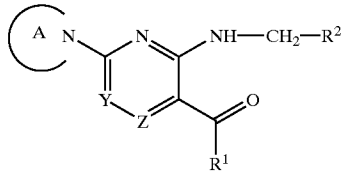
(57) **ABSTRACT**

An aromatic nitrogen-containing 6-membered cyclic compound of the formula (I):

(I)




wherein Ring A is a substituted or unsubstituted nitrogen-containing heterocyclic group; $R^1$ is a substituted or unsubstituted lower alkyl group, —NH—Q—$R^3$ ($R^3$ is a substituted or unsubstituted nitrogen containing heterocyclic group, and Q is a lower alkylene group or a single bond), or —NH—$R^4$ ($R^4$ is a substituted or unsubstituted cycloalkyl group); $R^2$ is a substituted or unsubstituted aryl group; one of Y and Z is =CH—, and the other is =N—, or a pharmaceutically acceptable salt thereof, these compounds exhibiting excellent selective PDE V inhibitory activities, and hence, being useful in the prophylaxis or treatment of penile erectile dysfunction, etc.

**22 Claims, No Drawings**

# AROMATIC NITROGEN-CONTAINING 6-MEMBERED CYCLIC COMPOUNDS

This application is a continuation application of PCT international application No. PCT/JP00/06258 which has an international filing date of Sep. 13, 2000 which designated the United States, the entire contents of which are incorporated by reference.

## TECHNICAL FIELD

The present invention relates to a novel aromatic nitrogen-containing 6-membered cyclic compound exhibiting a cGMP specific phosphodiesterase (PDE) inhibitory activity (PDE V inhibitory activity) and being useful as a medicament, and a process for preparing the same.

## BACKGROUND ART

In general, it is known that cGMP, which is an intracellular second messenger, is decomposed and inactivated by phosphodiesterase which widely distributes in many cell types and tissues of the living body, and when said PDE activity is inactivated, the level of cGMP in cells is increased, and as a result, various pharmacological activities, for example, relaxation of vascular smooth muscle, relaxation of bronchial smooth muscle, and inhibition of platelet aggregation are exhibited.

Moreover, it has been reported that such cGMP specific PDE inhibitors (i.e., PDE V inhibitors) are useful in the treatment of diseases caused by a functional disorder of cGMP-signaling, including hypertension, angina pectoris, myocardial infarction, chronic or acute heart failure, pulmonary hypertension, etc. (cf., PCT Patent Publication WO 96/05176, etc.), and prostatic hyperplasia (Australian Patent Publication No. 9955977). It has also been reported that PDE V inhibitors may be useful in the treatment of female sexual dysfunction (Vemulapalli et al., Life Sciences, 67, 23–29 (2000)), diabetic gastroparesis (Watkins et al., J. Clin. Invest. 106: 373–384 (2000)), achalasia (Bortolotti et al., Gastroenterology; 118: 253–257 (2000)), diarrhea (Mule et al., Br. J. Pharmacol., 127, 514–520 (1999)), constipation (Bakre et al., J. Cell. Biochem. 77: 159–167 (2000)) and asthma (Turner et al., Br. J. Pharmacol., 111, 1198–1204 (1994)).

Furthermore, it has been also reported that 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-phenylsulfonyl]-4-methylpiperazine [general name: Sildenafil] having PDE V inhibitory activity is useful in the treatment of diseases such as penile erectile dysfunction (copulative impotence), etc. (cf., Boolell et al., The Journal of Urology, Supplement, vol. 155, no. 5, p. 495A739 (1996); Terrett et al., Bioorganic & Medicinal Chemistry Letters, vol. 6, no. 15, p. 1819 (1996); and Ballard et al., British Journal of Pharmacology, Proceeding Supplement, vol. 118, p. 153 (1996)).

However, sildenafil has been reported to have side effects such as headache, facial suffusion, gut disorder, rhinitis, color sense disorder, penile erectile continuance, etc. (Irwin et al., The New England Journal of Medicine, vol. 338, no. 20, p. 1397–1404 (1998); Morales et al., International Journal of Impotence Research, vol. 10, no. 2, p. 69–73 (1998); and Goldenberg, Clinical Therapeutics, vol. 20, no. 6, p. 1033–1048 (1998)).

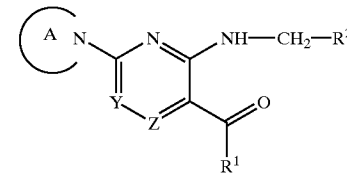
In addition, sildenafil has also been reported that the effects of sildenafil on light response of retina tissues and its PDE VI inhibitory activity correlate each other in the experiments on dogs (Morales et al., International Journal of Impotence Research, vol. 10, no. 2, p. 69–73 (1998)), while it has been reported that PDE VI on retina plays an importance role in the sensation of light (Morrales et al., International Journal of Impotence Research, vol. 10, no. 2, p. 69–73 (1998); Estrade et al., European Journal of Pharmacology, vol. 352, p. 157–163 (1998)).



## DISCLOSURE OF INVENTION

An object of the present invention is to provide a novel aromatic nitrogen-containing 6-membered cyclic compound showing an excellent phosphodiesterase V (PDE V) inhibitory activity, and being useful as a remedy for the prophylaxis or treatment of penile erectile dysfunction with few side effects. Another object of the present invention is to provide a process for preparing such a novel aromatic nitrogen-containing 6-membered cyclic compound.

The present invention relates to an aromatic nitrogen-containing 6-membered cyclic compound of the formula (I):




(I)

wherein Ring A is a substituted or unsubstituted nitrogen-containing heterocyclic group; $R^1$ is a substituted or unsubstituted lower alkyl group, a group of the formula: —NH—Q—$R^3$ (in which $R^3$ is a substituted or unsubstituted nitrogen-containing heterocyclic group, and Q is a lower alkylene group or a single bond), or a group of the formula: —NH—$R^4$ (in which $R^4$ is a substituted or unsubstituted cycloalkyl group); $R^2$ is a substituted or unsubstituted aryl group; one of Y and Z is a group of the formula: =CH—, and the other is a group of the formula: =N—, or a pharmaceutically acceptable salt thereof, and a process for preparing the same.

Among the compounds (I) of the present invention, the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- to 10-membered monocyclic or bicyclic nitrogen-containing heterocyclic group, more particularly, a 5- or 6-membered nitrogen-containing heteromonocyclic group and a 8- to 10-membered nitrogen-containing heterobicyclic group, and most particularly, a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group such as pyrrolidinyl group, piperazinyl group, piperidyl group, morpholino group, etc., a 5- or 6-membered aromatic nitrogen-containing heteromonocyclic group such as imidazolyl group, pyrrolyl group, etc., and a nitrogen-containing heterobicyclic group such as 6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl group, 5,6,7,8-tetrahydroimidazo[1,2-a]-pyrazin-7-yl group, 5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl group, 1,2,3,4-tetrahydro-2-isoquinolinyl group, 1H-2,3,4,5,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl group, 4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-6-yl group, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-6-yl group, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-3-yl group, etc.

The nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, for example, a 5- or 6-membered non-aromatic nitrogen-containing heteromono-

cyclic group such as morpholinyl group, piperazinyl group, piperidyl group, thiadiazolyl group, dihydropyrimidinyl group, dihydropyrazolyl group, a 5- or 6-membered aromatic nitrogen-containing heteromonocyclic group such as pyrimidinyl group, pyridazinyl group, pyridyl group, pyrazolyl group, imidazolyl group, oxazolyl group, thiazolyl group, pyrazinyl group, and a 8- to 10-membered nitrogen-containing heterobicyclic group such as benzothiazolyl group, quinolyl group, dihydrobenzoxazolyl group, etc.

The substituent of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A and $R^3$ is, for example, (1) a lower alkyl group, (2) a hydroxy-substituted lower alkyl group, (3) a formyl group, (4) an oxo group, (5) an amino group, (6) a di-(lower alkyl)amino group, (7) a hydroxy group, (8) a lower alkoxy group, (9) a lower alkoxycarbonyl group, (10) a lower alkoxy-substituted lower alkanoyl group, (11) a lower alkanoyl group, (12) a cyano-substituted lower alkyl group, and (13) a pyrimidinyl group substituted by (i) a benzylamino group substituted by a halogen atom and a lower alkoxy group and (ii) a cycloalkylcarbamoyl group substituted by a hydroxy group, etc.

The aryl group of the "substituted or unsubstituted aryl group" for $R^2$ is, for example, a 5- to 10-membered monocyclic or bicyclic aromatic hydrocarbon group such as phenyl group, naphthyl group, etc.

The substituent of the "substituted or unsubstituted aryl group" for $R^2$ is, for example, a lower alkoxy group, a halogen atom, a cyano group, a nitro group, a hydroxy group, a lower alkyl group, etc.

The substituent of the "substituted or unsubstituted lower alkyl group" for $R^1$ and the substituent of the "substituted or unsubstituted cycloalkyl group" for $R^4$ are, for example, a lower alkoxy group, a hydroxy group, a morpholinyl group, a lower alkylsulfonyl group, a di-(lower alkyl)phosphino group, a di-(lower alkyl)amino group, a pyrimidinyl-substituted lower alkylamino group, a pyridyl group, a pyridylamino group, a lower alkyl-substituted piperazinyl group, a pyrimidinyloxy group, etc.

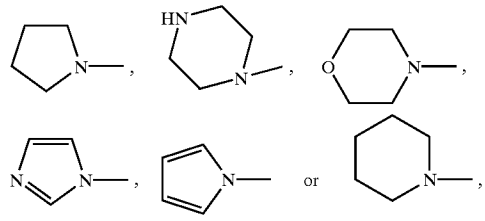
Throughout the present description and the claims, the "lower alkyl group" means a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, etc. The "lower alkoxy group" means a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropyloxy, butyloxy, isobutyloxy, tert-butyloxy, etc.

The "cycloalkyl group" means a cycloalkyl having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. The "lower alkylene group" means a straight chain or branched chain alkylene group having 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, etc.

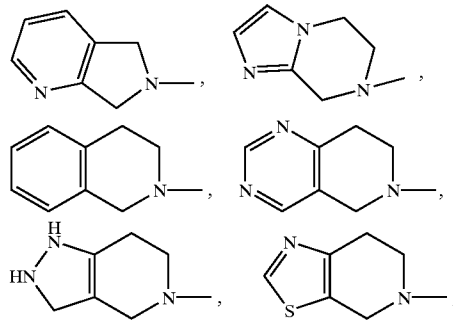
The "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom.

Among the compounds (I) of the present invention, preferable compounds are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of (1) a lower alkyl group, (2) a hydroxy-substituted lower alkyl group, (3) a formyl group, (4) an oxo group, (5) an amino group, (6) a hydroxy group, (7) a lower alkoxycarbonyl group, and (8) a pyrimidinyl group substituted by (i) a benzylamino group substituted by a halogen atom and a lower alkoxy group and (ii) a cycloalkylcarbamoyl group substituted by a hydroxy group, $R^1$ is a lower alkyl group which may optionally be substituted by a group selected from the group consisting of a lower alkoxy group, a hydroxy group, a morpholinyl group, a lower alkylsulfonyl group, a di-(lower alkyl)phosphino group, a di-(lower alkyl) amino group, a pyrimidinyl-substituted lower alkylamino group, a pyridyl group, a pyridylamino group, and a lower alkyl-substituted piperazinyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, an amino group, a di-(lower alkyl)amino group, a lower alkanoyl group and a cyano-substituted lower alkyl group, $R^4$ is a cycloalkyl group being substituted by a group selected from the group consisting of hydroxy group, a lower alkoxy group and a pyrimidinyloxy group, $R^2$ is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group, a halogen atom, a cyano group, a nitro group, a hydroxy group and a lower alkyl group.

More particularly, preferable compounds of the present invention are compounds of the formula (I), wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group of the formula:



or a nitrogen-containing heterobicyclic group of the following formula wherein the above-mentioned 5- or 6-membered nitrogen-containing heteromonocyclic group and a 5- or 6-membered cyclic group are fused:



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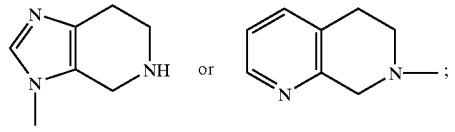
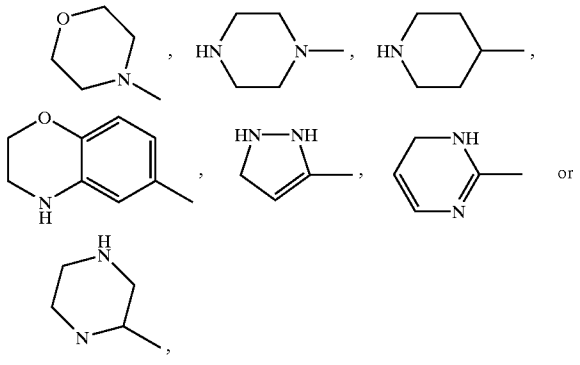
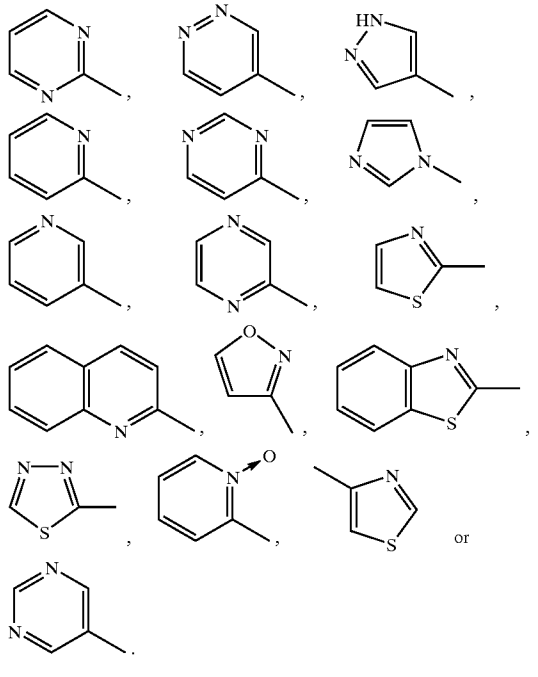


and the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



or an aromatic nitrogen-containing heterocyclic group of the formula:

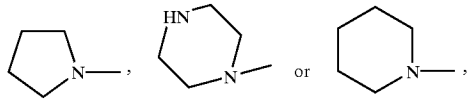


Among the compounds (I) of the present invention, other preferable compounds are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, a formyl group and an oxo group, $R^1$ is

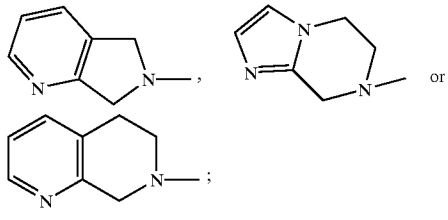


a lower alkyl group which may optionally be substituted by a group selected from the group consisting of a lower alkoxy group and a morpholinyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, $R^4$ is a cycloalkyl group being substituted by a group selected from the group consisting of hydroxy group and a lower alkoxy group, $R^2$ is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group, a halogen atom and a cyano group.

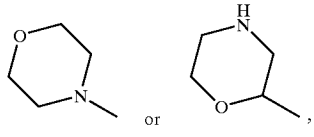
More particularly, preferable compounds of the present invention are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



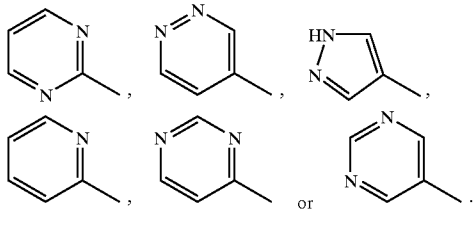
or a nitrogen-containing heterobicyclic group of the following formula wherein the above-mentioned 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group and a 5- or 6-membered aromatic nitrogen-containing heteromonocyclic group are fused:



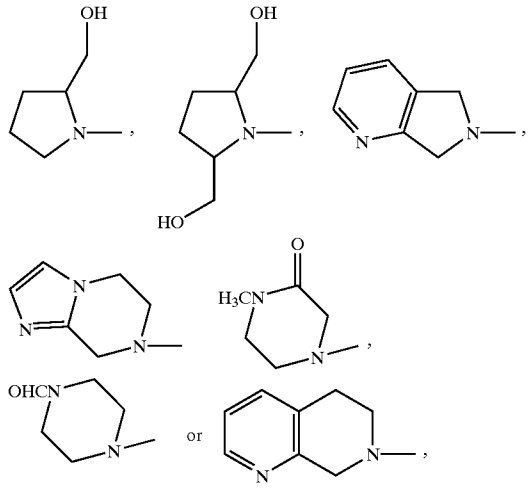
and the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



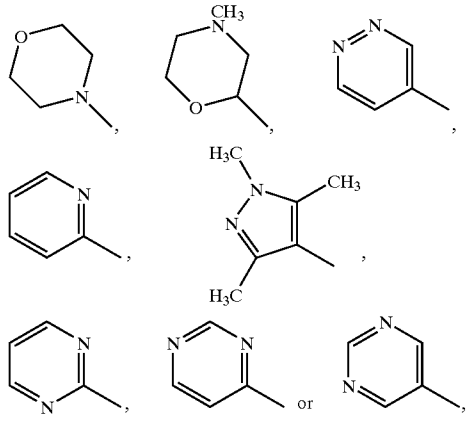
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



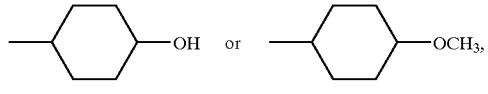
More particularly, preferable compounds of the present invention are compounds of the formula (I) wherein Ring A is a group of the formula:



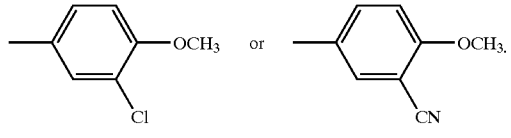
$R^1$ is a lower alkyl group, a lower alkoxy-substituted lower alkyl group, a morpholinyl-substituted lower alkyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, $R^3$ is a group of the formula:



$R^4$ is a group of the formula:

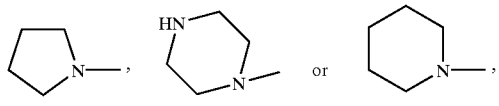


and $R^2$ is a group of the formula:

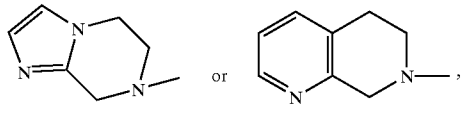


Among the compounds (I) of the present invention, more preferable compounds are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is a group selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, a formyl group and an oxo group, $R^1$ is a lower alkoxy-substituted lower alkyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, $R^4$ is a hydroxy-substituted cycloalkyl group, and $R^2$ is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group and a halogen atom.

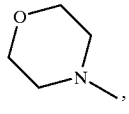
More particularly, more preferable compounds of the present invention are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



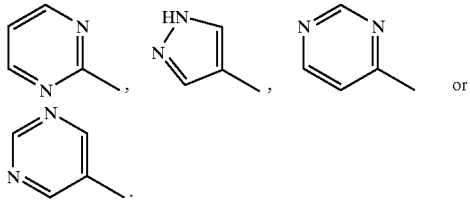
or a group of the formula:



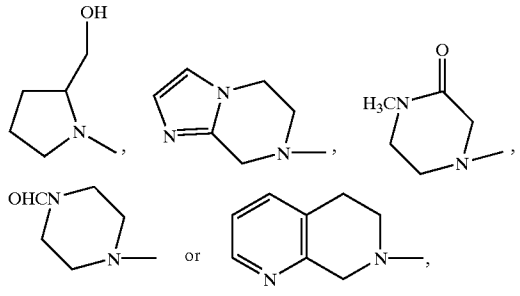
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



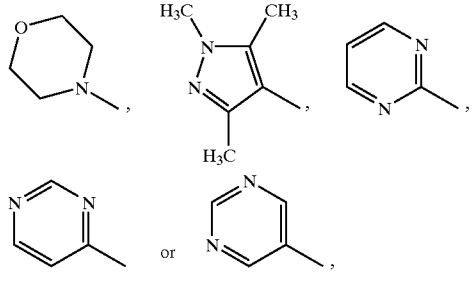
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



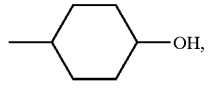
More particularly, more preferable compounds of the present compounds are compounds of the formula (I) wherein Ring A is a group of the formula:



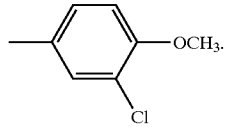
$R^1$ is a lower alkoxy-substituted lower alkyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, $R^3$ is a group of the formula:



$R^1$ is a group of the formula:

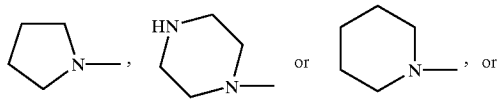


and $R^2$ is a group of the formula:

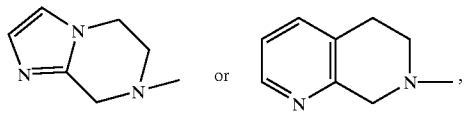


Among the compounds (I) of the present invention, further preferable compounds are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is a hydroxy-substituted lower alkyl group, $R^1$ is a group of the formula: —NH—Q—$R^3$, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^1$ is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, and $R^2$ is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group and a halogen atom.

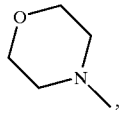
More particularly, the more preferable compounds of the present invention are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



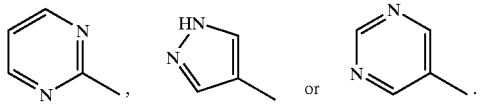
or a group of the formula:



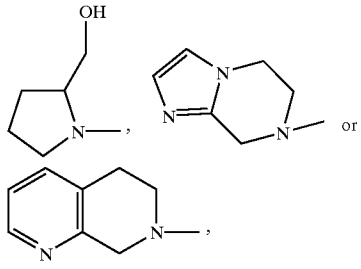
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



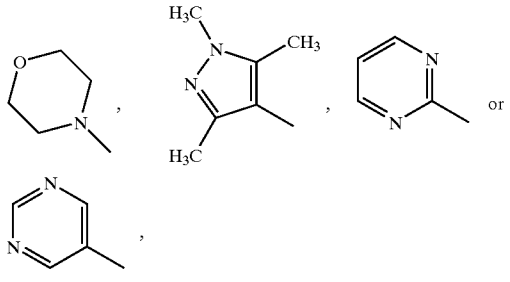
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



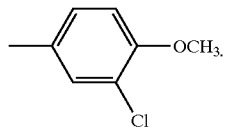
More particularly, the preferable compounds of the present invention are compounds of the formula (I), wherein Ring A is a group of the formula:



$R^1$ is a group of the formula: —NH—Q—$R^3$, $R^3$ is a group of the formula:



and $R^2$ is a group of the formula:




Among the compounds (I) of the present invention, the most preferable compounds are compounds of the formula (I) wherein Y is a group of the formula: ═N—, and Z is a group of the formula: ═CH—.

Among the compounds (I) of the present invention, pharmaceutically preferable compounds are compounds selected from the following group or a pharmaceutically acceptable salt thereof.

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-methoxycyclohexyl)carbamoyl]-pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]-pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]-pyrimidine;

2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl]-pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(4-methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(4-formyl-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]-pyrimidine;

2-[cis-2,5-bis(hydroxymethyl)-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-acethylpyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyridazinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl) carbamoyl]pyrimidine;

(S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-[2-hydroxymethyl-1-pyrrolidinyl]pyrazine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl) carbonyl] pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(4-methyl-2-morpholinyl) methyl]-carbamoyl]pyrimidine;

(S)-2-[N-(2-morpholinoethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine;

2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrazine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl] pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

Among the compounds (I) of the present invention, pharmaceutically more preferable compounds are compounds selected from the following group or a pharmaceutically acceptable salt thereof.

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(4-methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(4-formyl-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl] pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

Among the compounds (I) of the present invention, pharmaceutically preferable other compounds are compounds

selected from the following group or a pharmaceutically acceptable salt thereof.

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine;

(S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine;

(S)-2-[N-(2-morpholinoethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

Among the compounds (I) of the present invention, especially pharmaceutically preferable compounds are compounds selected from the following group or a pharmaceutically acceptable salt thereof.

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof, 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof; and further (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

When the compound (I) of the present invention or a pharmaceutically acceptable salt thereof has an asymmetric carbon atom at Ring A, $R^1$ and/or $R^2$, it may exist in the form of an optically active isomer thereof owing to said asymmetric carbon atom thereof, and the present invention also includes these optical isomers and a mixture thereof.

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof exhibits an excellent selective PDE V inhibitory activity but substantially shows few side effects such as color sense disorder, and hence, it can be used in the prophylaxis or treatment of penile erectile dysfunction.

The present compound (I) can clinically be used either in the free form or in the form of a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt of the compound (I) includes a salt with an inorganic acid such as hydrochloride, sulfate, nitrate or hydrobromide, or a salt with an organic acid such as acetate, fumarate, oxalate, citrate, methanesulfonate, benzenesulfonate, tosylate, or maleate.

The present compound (I) or a salt thereof includes either intramolecular salt or an additive thereof, and solvates or hydrates thereof.

The present compound (I) or a pharmaceutically acceptable salt thereof can be administered either orally or parenterally, and can be formulated into a conventional pharmaceutical preparation such as tablets, granules, fine granules, pills, capsules, powders, injections, inhalants, buccal preparation, sublingual tablets, syrups, dry syrups, jellys, suppositories, ointments, elixirs, liniments, lotions, drinks, nasal drops, percutaneous preparations, and rapidly-disintegrating tablets in oral cavity, etc. These pharmaceutical preparations may be prepared by formulating with a pharmaceutically acceptable additive such as excipient, binder, wetting agent, disintegrator, thickening agent, etc., by a conventional method.

The dose of the compound (I) of the present invention or a pharmaceutically acceptable salt thereof may vary in accordance with the administration routes, and the ages, weights and conditions of the patients. For example, when administered in an injection preparation, it is usually in the range of about 0.001–100 mg/kg/day, preferably in the range of about 0.1–10 mg/kg/day. When administered in an oral preparation, it is usually in the range of about 0.1–200 mg/kg/day, preferably in the range of about 0.1–80 mg/kg/day.

Concomitantly, since the compound (I) of the present invention or a pharmaceutically acceptable salt thereof exhibits an excellent selective PDE V inhibitory activity, it also may be useful in the prophylaxis or treatment of diseases caused by a functional disorder of cGMP-signaling, such as pulmonary hypertension, diabetic gastroparesis, hypertension, angina pectoris, myocardial infarction, chronic or acute heart failure, female sexual dysfunction, prostatic hyperplasia, asthma, diarrhea, constipation and achalasia in addition to the above-mentioned erectile dysfunction.

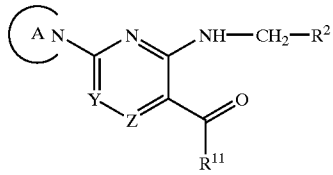
## BEST MODE FOR CARRYING OUT THE INVENTION

The compounds (I) of the present invention may be prepared by the following Processes A to F.

Process A

Among the compounds (I) of the present invention, the compound of the formula (I) wherein $R^1$ is a group of the formula: —NH—Q—$R^3$ or —NH—$R^4$, i.e., the compound of the formula (I-a):

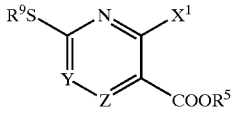
(I-a)




(wherein $R^{11}$ is a group of the formula: —NH—Q—$R^3$ or —NH—$R^4$, and the other symbols are as defined above) can be prepared by

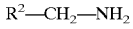
reacting a compound of the formula (II):

(II)




wherein $X^1$ is a halogen atom, $R^5$ is a protecting group for carboxyl group, $R^9$ is substituted or unsubstituted lower alkyl group or a substituted or unsubstituted aryl group, and the other symbols are as defined above,

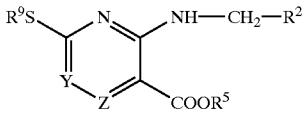
with a compound of the formula (III):



(III)

wherein the symbols are as defined above,

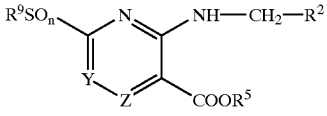
oxidizing the resulting compound of the formula (IV):



(IV)

wherein the symbols are as defined above,

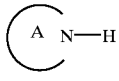
to give a sulfonyl (or sulfinyl) compound of the formula (V):



(V)

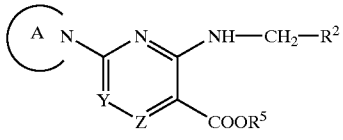
wherein n is 1 or 2, and the other symbols are as defined above,

reacting the compound (V) with a compound of the formula (VI):



(VI)

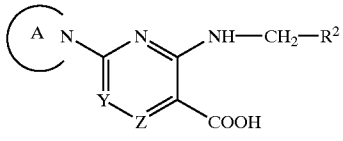
wherein the symbol is as defined above, or a salt thereof, to give a compound of the formula (VII):



(VII)

wherein the symbols are as defined above,

removing a protecting group $R^5$ for a carboxyl group of the compound (VII) to give a compound of the formula (VIII):



(VIII)

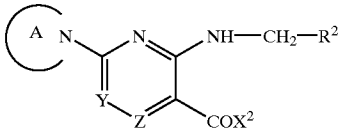
wherein the symbols are as defined above, and

followed by reacting the compound (VIII) with a compound of the formula (IX-a):

(IX-a)

wherein the symbols are as defined above.

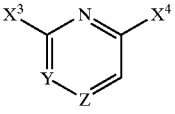
The compound (I-a) can also be prepared by subjecting the compound (VIII) to halogenation to give a compound of the formula (X):



(X)

wherein $X^2$ is a halogen atom, and the other symbols are as defined above, and followed by reacting the compound (X) with the compound (IX-a).

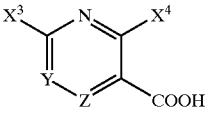
In addition, the above compound (VII) can also be prepared by treating a dihalogeno compound of the formula (XI):



(XI)

wherein $X^3$ and $X^4$ are a halogen atom, and the other symbols are as defined above, with carbon dioxide,

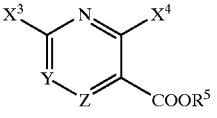
protecting the carboxyl group of the resulting compound of the formula (XII):



(XII)

wherein the symbols are as defined above,

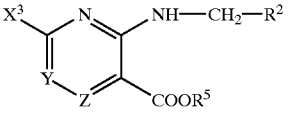
to give a compound of the formula (XIII):



(XIII)

wherein the symbols are as defined above,

reacting the compound (XIII) with the compound (III) to give a compound of the formula (XIV):



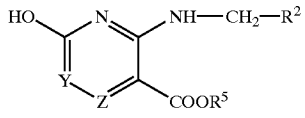
(XIV)

wherein the symbols are as defined above, and

followed by reacting the compound (XIV) with the compound (VI).

Further, the above compound (XIV) can also be prepared by subjecting the compound (V) to hydrolysis, followed by halogenating the resulting compound of the formula (XV):

(XV)

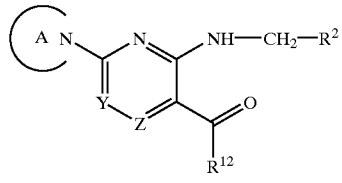


wherein the symbols are as defined above.

to Process B

Among the compounds (I) of the present invention, the compound of the formula (I) wherein $R^1$ is a substituted or unsubstituted lower alkyl group, i.e., the compound of the formula (I-b):

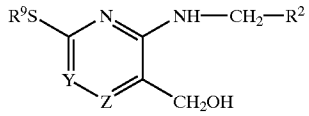
(I-b)



(wherein $R^{12}$ is a substituted or unsubstituted lower alkyl group, and the other symbols are as defined above) can be prepared by

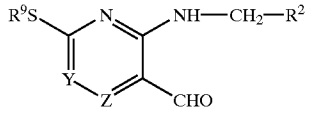
oxidizing a compound of the formula (XVI):

(XVI)



wherein the symbols are as defined above, which is obtained by reduction of the compound (IV), to give a compound of the formula (XVII):

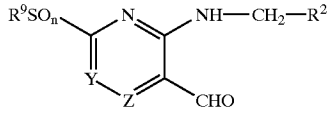
(XVII)



wherein the symbols are as defined above,

further oxidizing the compound (XVII) to give a compound of the formula (XVIII):

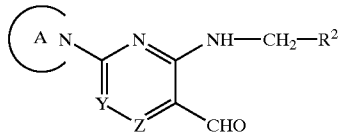
(XVIII)



wherein the symbols are as defined above,

reacting the compound (XVIII) with the compound (VI) to give a compound of the formula (XIX):

(XIX)



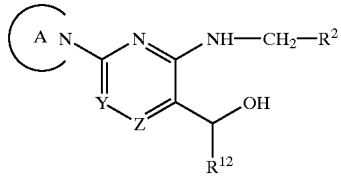
wherein the symbols are as defined above,

reacting the compound (XIX) with a metal salt of a compound of the formula (IX-b):

$$R^{12}—H \qquad \text{(IX-b)}$$

wherein $R^{12}$ is as defined above, to give a compound of the formula (XX):

(XX)

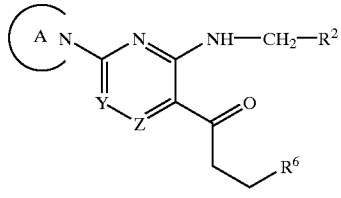


wherein the symbols are as defined above,

followed by oxidizing the compound (XX).

In addition, among the compounds (I) of the present invention, the compound of the formula (I) wherein a group $R^1$ is a lower alkoxy-substituted ethyl group, a morpholino-substituted ethyl group, a 4-lower alkylpiperazinyl group-substituted ethyl group, a 3-pyridylamino-substituted ethyl group, a 2-pyridyl-lower alkylamino group-substituted ethyl group, a di-lower alkylaminoethyl group or a hydroxyethyl group, i.e., the compound of the formula (I-c):

(I-c)

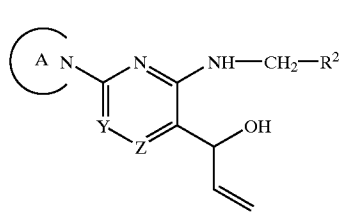


wherein $R^6$ is a lower alkoxy group, a morpholino group, a 4-lower alkylpiperazinyl group, a 3-pyridylamino group, a 2-pyrimidyl-lower alkylamino group, a di-lower alkylamino group or a hydroxy group, and the other symbols are as defined above,

can be prepared by reacting the compound (XIX) with a Grignard compound of the formula:

$$CH_2=CHMgBr \qquad \text{(XXI)}$$

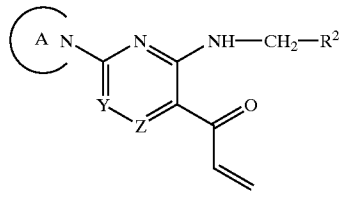
to give a compound of the formula (XXII):



(XXII)

wherein the symbols are as defined above,

oxidizing the compound (XXII) to give a compound of the formula (XXIII):



(XXIII)

wherein the symbols are as defined above,

followed by reacting the compound (XXIII) with a compound of the formula (XXIV):

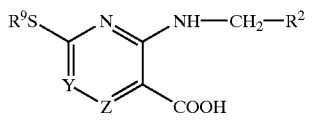
$R^6$—H (XXIV)

wherein $R^6$ is as defined above.

Process C

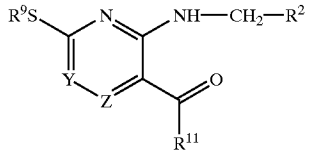
The compound (I-a) can be prepared by

reacting a compound of the formula (XXV):



(XXV)

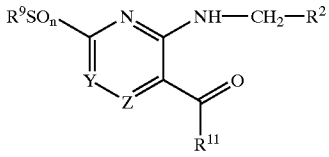
wherein the symbols are as defined above, which is obtained by removing the protecting group $R^5$ for a carboxyl group of the compound (IV), with the compound (IX-a) to give a compound of the formula (XXVI-a):



(XXVI-a)

wherein the symbols are as defined above,

oxidizing the compound (XXVI-a) to give a compound of the formula (XXVII-a):



(XXVII-a)

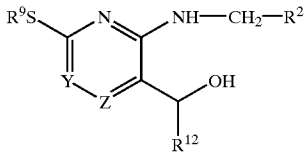
wherein the symbols are as defined above,

followed by reacting the compound (XXVII-a) with the compound (VI).

Process D

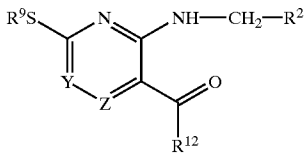
The compound (I-b) can be prepared by

oxidizing a compound of the formula (XXVIII):



(XXVIII)

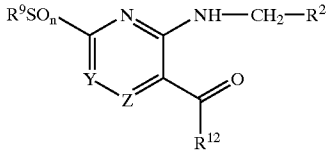
wherein the symbols are as defined above, which is obtained by reacting the compound (XVII) with a metal salt of the compound (IX-b), to give a compound of the formula (XXVI-b):



(XXVI-b)

wherein the symbols are as defined above,

further oxidizing the compound (XXVI-b) to give a compound of the formula (XX)VII-b):



(XXVII-b)

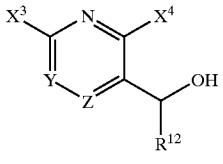
wherein the symbols are as defined above,

followed by reacting the compound (XXVII-b) with the compound (VI).

Process E

The compound (I-b) can be prepared by

oxidizing a compound of the formula (XXX):



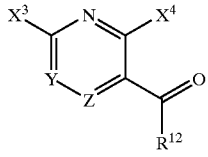
(XXX)

wherein the symbols are as defined above, which is obtained by reacting the dihalogeno compound (XI) with a compound of the formula (XXIX):

$R^{12}$—CHO (XXIX)

wherein $R^{12}$ is as defined above, to give a compound of the formula (XXXI):

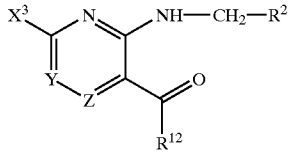
(XXXI)



wherein the symbols are as defined above,

reacting the compound (XXXI) with the compound (III) to give a compound of the formula (XXXII):

(XXXII)

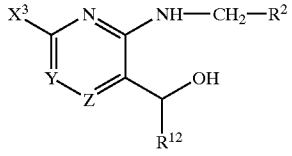


wherein the symbols are as defined above,

followed by reacting the compound (XXXII) with the compound (VI).

The above compound (XXXII) can also be prepared by reacting the compound (XXX) with the compound (III) to give a compound of the formula (XXXIII):

(XXXIII)



wherein the symbols are as defined above,

followed by oxidizing the compound (XXXIII).

Process F

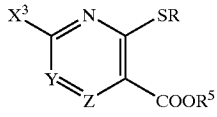
The compound (I-a) can be prepared by

reacting the compound (XIII) with a compound of the formula (XXXIV):

RSH (XXXIV)

wherein R is a substituted or unsubstituted lower alkyl group or a substituted or unsubstituted aryl group, to give a compound of the formula (XXXV):

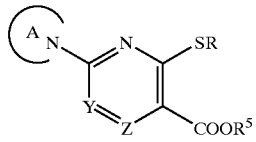
(XXXV)



wherein the symbols are as defined above,

reacting the compound (XXXV) with the compound (VI) or a salt thereof to give a compound of the formula (XXXVI):

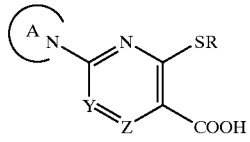
(XXXVI)



wherein the symbols are as defined above,

removing the protecting group $R^5$ for a carboxyl group of the compound (XXXVI) to give a compound of the formula (XXXVII):

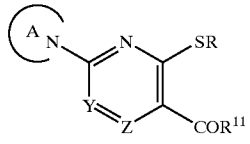
(XXXVII)



wherein the symbols are as defined above,

reacting the compound (XXXVII) with the compound (IX-a) to give a compound of the formula (XXXIX):

(XXXIX)



wherein the symbols are as defined above,

subjecting the compound (XXXIX) to oxidation to give a sulfonyl or sulfinyl compound,

followed by reacting the resultant with the compound (III).

The above Processes A to F can be carried out as follows.

Process A

The reaction of the compound (II) with the compound (III) is carried out in the presence or absence of an acid scavenger in a solvent. The acid scavenger includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc., and an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The solvent may be any solvents which do not disturb the reaction, for example, dimethylsulfoxide, tetrahydrofuran, toluene, ethyl acetate, chloroform, dimethoxyethane, xylene, N,N-dimethylformamide, etc. The reaction is carried out at a temperature of from −10° C. to room temperature, preferably at a temperature of from 0° C. to room temperature.

The reaction of oxidizing the compound (IV) to give the sulfonyl (or sulfinyl) compound (V) is carried out in the presence of an oxidizing agent in a solvent. The oxidizing agent includes, for example, peracids such as m-chloroperbenzoic acid, peracetic acid, etc., and an inorganic oxidizing agent such as manganese dioxide, sodium periodate, hydrogen peroxide, dinitrogen tetroxide, halogen, hydroperoxide, iodobenzene acetate, t-butyl hypochlorite, sulfuryl chloride, potassium peroxymonosulfate, etc. The solvent may be any solvent which does not disturb the reaction, for example, chloroform, methylene chloride, dichloroethane, acetic acid, etc. The reaction is carried out at a temperature of from −78° C. to 50° C., preferably at a temperature of from −10° C. to 10° C.

The reaction of the compound (V) with the compound (VI) or a salt thereof can be carried out in the presence or absence of an acid scavenger in a solvent. The acid scavenger includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc., and an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The salt of the compound (VI) is preferably an alkali metal salt such as sodium salt, potassium salt, etc. The solvent may be any solvent which does not disturb the reaction, for example, N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane, dimethylsulfoxide, etc. The reaction is carried out at a temperature of from 0° C. to 150° C., preferably at a temperature of from room temperature to 60° C.

The reaction of removing the protecting group $R^5$ for a carboxyl group of the compound (VII) to give the compound (VIII) can be carried out by a conventional method such as hydrolysis, catalytic reduction, etc. which is selected according to the types of the protecting group for a carboxyl group to be removed. When a protecting group for a carboxyl group is removed by hydrolysis, the hydrolysis is carried out, for example, in the presence of a base in a solvent. The base is preferably, for example, an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, lithium hydroxide, etc., or an alkali metal carbonate such as sodium carbonate, potassium carbonate, etc. The solvent may be water or a mixture of water and methanol, ethanol, tetrahydrofuran, dioxane, N,N-dimethyformamide, dimethylsulfoxide, etc. The reaction is carried out at a temperature of from 0 to 80° C., preferably at a temperature of from 5° C. to 60° C. The protecting group for a carboxyl group represented by $R^5$ may be any conventional protecting group for a carboxyl group, such as a lower alkyl group, benzyl group, etc.

The reaction of the compound (VIII) with the compound (IX-a) can be carried out in the presence or absence of a condensing agent, a base or an activating agent in a suitable solvent. The condensing agent includes, for example, dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diphenylphosphoryl azide, diethylcyanophosphonate, etc., which is usually used in the peptide synthesis. The base includes, for example, an organic base such as triethylamine, N-methymorpholine, etc., and the activating agent includes, for example, 1-hydroxybenzotriazole, etc. The solvent may be any solvent which does not disturb the reaction, for example, methylene chloride, tetrahydrofuran, N,N-dimethylformamide, acetonitrile, N,N-dimethylacetamide, ethyl acetate, etc. The reaction is carried out at a temperature of from −30° C. to 50° C., preferably at a temperature of from −10° C. to 10° C.

The alternative process of converting the compound (VIII) into the compound (X), which is further reacted with the compound (IX-a) can be carried out by firstly reacting the compound (VIII) with a halogenating agent in the presence or absence of an activating agent by a conventional method, and reacting the resulting compound (X) with the compound (IX-a). The reaction of the compound (VIII) with a halogenating agent is carried out in a solvent. The halogenating agent is preferably thionyl chloride, oxalyl chloride, phosphorus pentachloride, etc. The activating agent is preferably an amide compound such as N,N-dimethylformamide, etc. The solvent may be any solvent which does not disturb the reaction, for example, methylene chloride, chloroform, tetrahydrofuran, benzene, toluene, dioxane, etc. The reaction is carried out at a temperature of from −30° C. to 100° C., preferably at a temperature of from −5° C. to 10° C.

The subsequent reaction with the compound (IX-a) is carried out in the presence of an acid scavenger in a solvent. The acid scavenger includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, dimethylaminopyridine, etc., and an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, methylene chloride, chloroform, toluene, benzene, dioxane, ethyl acetate, etc. The reaction is carried out at a temperature of from −30° C. to 100° C., preferably at a temperature of from −5° C. to 10° C.

The reaction of treating the dihalogeno compound (XI) with carbon dioxide to give the compound (XII) can be carried out in the presence of a base in a solvent. The base includes, for example, an alkali metal salt of an organic base such as lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidide, etc. The solvent may be any to solvent which does not disturb the reaction, for example, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, etc. The reaction is carried out at a temperature of from −100° C. to −30° C., preferably at a temperature of from −100° C. to −70° C.

The reaction of protecting the carboxyl group of the compound (XII) to give the compound (XIII) can be carried out by a conventional method, for example, by reacting with an alkylating agent in the presence of a base in a solvent, when the protecting group is a lower alkyl group. The alkylating agent is preferably a lower alkyl halide such as methyl iodide. The base is preferably an alkali metal hydrogen carbonate such as sodium hydrogen carbonate, and the solvent may be any solvent which does not disturb the reaction, for example, N,N-dimethylformamide, tetrahydrofuran, etc. The reaction is carried out at a temperature of from 0° C. to 100° C., preferably at a temperature of from room temperature to 70° C.

The reaction of the compound (XIII) with the compound (III) to give the compound (XIV) can be carried out in the same manner as in the reaction of the compound (II) with the compound (III).

The reaction of the compound (XIV) with the compound (VI) to give the compound (VII) can be carried out in the same manner as in the reaction of the compound (V) with the compound (VI).

The hydrolysis reaction of the compound (V) to give the compound (XV) can be carried out in the presence of a base in a solvent. The base includes, for example, an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, lithium hydroxide, etc., and an alkali metal carbonate such as sodium carbonate, potassium carbonate, etc. The solvent is preferably water, or a mixture of water and methanol, ethanol, tetrahydrofuran, dioxane, N,N-dimethylformamide, dimethylsulfoxide, etc. The reaction is carried out at a temperature of from −20° C. to 80° C., preferably at a temperature of from −5° C. to 60° C.

The reaction of halogenating the compound (XV) to give the compound (XIV) can be carried out in the same manner as in the reaction of obtaining the compound (X) by halogenating the compound (XIII) by a halogenating agent.

Process B

The reduction reaction of the compound (IV) to give the compound (XVI) can be carried out in the presence of a reducing agent in a suitable solvent. The reducing agent is preferably an alkali metal aluminum hydride such as lithium

aluminum hydride, and an alkali metal borohydride such as lithium borohydride, etc. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane, etc. The reaction is carried out at a temperature of from −78° C. to a boiling point of the solvent to be used, preferably at a temperature of from −10° C. to room temperature.

The oxidation reaction of the compound (XVI) to give the compound (XVII) can be carried out in the presence of an oxidizing agent in a solvent. The oxidizing agent may be any one which can convert an alcohol into a carbonyl compound, for example, manganese dioxide, barium permanganate, potassium permanganate, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, pyridinium chlorochromate, pyridinium dichloromate, etc. The solvent may be any solvent which does not disturb the reaction, for example, chloroform, toluene, ethyl acetate, 1,2-dichloroethane, methylene chloride, tetrahydrofuran, etc. The reaction is carried out at a temperature of from 0° C. to 100° C., preferably at a temperature of from room temperature to 70° C.

The oxidation reaction of the compound (XVII) to give the compound (XVIII) is carried out in the same manner as in the reaction of obtaining the compound (V) by oxidizing the compound (IV).

The reaction of the compound (XVIII) with the compound (VI) to give the compound (XIX) is carried out in the same manner as in the reaction of the compound (V) with the compound (IV).

The reaction of the compound (XIX) with a metal salt of the compound (IX-b) to give the compound (XX) may be carried out in a suitable solvent. The metal salt of the compound (IX-b) is preferably lithium salt, etc. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane, etc. The reaction may preferably proceed at a temperature of from −78° C. to room temperature.

The oxidation reaction of the compound (XX) to give the compound (I-b) may be carried out in the same manner as in the reaction of obtaining (XVII) by oxidizing the compound (XVI).

The reaction of the compound (XIX) with the Grignard compound can be carried out in a suitable solvent. The solvent is preferably tetrahydrofuran, dioxane, diethyl ether, etc. The reaction may preferably proceed at a temperature of from −78° C. to 60° C., preferably at a temperature of from −78° C. to room temperature.

The oxidation reaction of the compound (XXII) to give the compound (XXIII) is carried out in the same manner as in the reaction of obtaining the compound (XVII) by oxidizing the compound (XVI).

The reaction of the compound (XXIII) with the compound (XXIV) wherein $R^6$ is a morpholino group, a 4-lower alkylpiperazinyl group, a 3-pyridylamino group, a 2-pyrimidyl-lower alkylamino group, or a di-lower alkylamino group to give the compound (I-c) wherein $R^6$ is a morpholino group, a 4-lower alkylpiperazinyl group, a 3-pyridylamino group, a 2-pyrimidinyl-lower alkylamino group, or a di-lower alkylamino group can be carried out in the presence or absence of a base in a suitable solvent. The base includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc., and an inorganic base such as sodium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The solvent may preferably be ethanol, N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane, dimethylsulfoxide, etc. The reaction may preferably proceed at a temperature of from 0° C. to 150° C., preferably at a temperature of from room temperature to 60° C.

On the other hand, the reaction of the compound (XXIII) with the compound (XXIV) wherein $R^6$ is a hydroxy group or a lower alkoxy group to give the compound (XXI) wherein $R^6$ is a hydroxy group or a lower alkoxy group can be carried in the presence of an acid in a solvent or without a solvent. The acid includes, for example, an inorganic acid such as sulfuric acid, etc., or an organic acid such as methanesulfonic acid, camphorsulfonic acid, toluenesulfonic acid, benzenesulfonic acid, etc. The solvent may preferably be diethyl ether, toluene, benzene, N,N-dimethylformamide, dimethoxyethane, dimethylsulfoxide, etc. The reaction may preferably proceed at a temperature of from 0° C. to 150° C., preferably at a temperature of from room temperature to 60° C.

Process C

The reaction of removing the protecting group $R^5$ for a carboxyl group of the compound (IV) to give the compound (XXV) can be carried out in the same manner as in the reaction of obtaining the compound (VIII) by removing the protecting group $R^5$ for a carboxyl group of the compound (VII).

The reaction of the compound (XXV) with the compound (IX-a) to give the compound (XXVI-a) can be carried out in the same manner as in the reaction of the compound (VIII) with the compound (IX-a).

The reaction of oxidizing the compound (XXVI-a) to give the compound (XXVII-1) can be carried out in the same manner as in the reaction of obtaining the compound (V) by oxidizing the above compound (IV).

The reaction of the compound (XXVII-a) with the compound (VI) to give the compound (I-a) of the present invention can be carried out in the same manner as in the reaction of the compound (V) with the compound (VI).

Process D

The reaction of the compound (XVII) with a metal salt of the compound (IX-b) to give the compound (XXVIII) can be carried out in the same manner as in the reaction of the compound (XIX) with a metal salt of the compound (IX-b).

The reaction of oxidizing the compound (XXVIII) to give the it compound (XXVI-b) can be carried out in the same manner as in the reaction of obtaining the compound (XVII) by oxidizing the compound (XVI).

The process wherein the compound (XXVI-b) is oxidized to give the compound (XXVII-b) which is further converted into the compound (I-b) of the present invention can be carried out in the same manner as in the process wherein the compound (XXVI-a) is oxidized to give the compound (XXVII-a) which is further converted into the compound (I-a) of the present invention.

Process E

The reaction of the compound (XI) with the compound (XXIX) to give the compound (XXX) is carried out in the presence of a base in a suitable solvent. The base includes, for example, an alkali metal salt of an organic base such as lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidide, etc. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, etc. The reaction is carried out at a temperature of from −100° C. to −30° C., preferably at a temperature of from −100° C. to −70° C.

The reaction of oxidizing the compound (XXX) to give the compound (XXXI) can be carried out in the same manner as in the reaction of oxidizing the compound (XVI) to give the compound (XVII).

The reaction of the compound (XXXI) with the compound (III) to give the compound (XXXII) can be carried out

in the same manner as in the reaction of the compound (II) with the compound (III).

The reaction of the compound (XXXII) with the compound (VI) or a salt thereof to give the compound (I-b) of the present invention can be carried out in the same manner as in the reaction of the compound (V) with the compound (VI).

The reaction of the compound (XXX) with the compound (III) to give the compound (XXXIII) can be carried out in the same manner as in the reaction of the compound (II) with the compound (III). Besides, the reaction of oxidizing the compound (XXXIII) to give the compound (XXXII) can be carried out in the same manner as in the reaction of oxidizing the compound (XVI) to give the compound (XVII).

Process F

The reaction of the compound (XIII) with the compound (XXXIV) can be carried out in the presence or absence of an acid scavenger in a solvent. The acid scavenger includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc., or an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The solvent may be any solvent which does not disturb the reaction, for example, N,N-dimethylformamide, tetrahydrofuran, toluene, ethyl acetate, chloroform, dimethoxyethane, xylene, dimethylformamide, etc. The reaction is carried out at a temperature of from −10° C. to room temperature, preferably at a temperature of from 0° C. to room temperature.

The reaction of the compound (XXXV) with the compound (VI) or a salt thereof can be carried out in the same manner as in the reaction of the compound (V) with the compound (VI).

The reaction of removing the protecting group $R^5$ for a carboxyl group of the compound (XXXVI) to give the compound (XXXVII) can be carried out in the same manner as in the reaction of removing the protecting group $R^5$ for a carboxyl group of the compound (VII) to give the compound (VIII).

The reaction of the compound (XXXVII) with the compound (IX-a) can be carried out in the same manner as in the reaction of the compound (VIII) with the compound (IX-a).

The oxidation reaction of the compound (XXXIX) can be carried out in the same manner as the reaction of the compound (IV) to give the compound (V). The oxidating agent is preferably m-chloroperbenzoic acid, etc. The solvent may be any solvent which does not disturb the reaction, for example, chloroform, methylene chloride, dichloroethane, acetic acid, etc. The reaction is carried out at a temperature of from −78° C. to 50° C., preferably at a temperature of from −10° C. to 10° C.

The subsequent reaction with the compound (III) can be carried out in the same manner as in the reaction of the compound (II) and the compound (III).

The compound (I) thus obtained can be converted into a pharmaceutically acceptable salt thereof.

The starting compound (II) can be prepared, for example, according to the method disclosed in Journal of American Chemical Society, p. 350, vol. 65, 1943.

Examples of the compound (I) of the present invention which can be prepared by the above exemplified methods are illustrated below, but the present invention should not be construed to be limited thereto.

## EXAMPLE 1

(1) To a solution of 4-chloro-5-ethoxycarbonyl-2-methylthiopyrimidine (25.33 g) in N,N-dimethylformamide (85 ml) are added a solution of 3-chloro-4-methoxybenzylamine (19.62 g) in N,N-dimethylformamide (15 ml) and triethylamine (16.7 ml) under ice-cooling. The mixture is stirred at room temperature for 20 minutes, and thereto is added 3-chloro-4-methoxybenzylamine (940 mg), and the mixture is further stirred for 15 minutes. To the mixture is further added said amine (940 mg), and the mixture is stirred for 15 minutes. The reaction mixture is poured into a mixture of ice water and citric acid, and the mixture is extracted with ethyl acetate. The extract is washed successively with a 10% aqueous citric acid solution, water and brine, and dried over anhydrous sodium sulfate. The solvent is evaporated under reduced pressure, and the residue is washed with n-hexane to give 4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-methylthiopyrimidine (38.34 g), m.p. 86° C.

(2) To a solution of the compound (5.00 g) obtained in the above (1) in chloroform (50 ml) is added a solution of m-chloroperbenzoic acid (4.00 g) in chloroform (50 ml) under ice-cooling, and the mixture is stirred for 2 hours. The reaction mixture is washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and the organic layer is dried over anhydrous sodium sulfate, and the solvent is evaporated under reduced pressure to give crude 4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-methylsulfinylpyrimidine, MS (m/z): 447 ($MH^+$).

(3) The crude product obtained in the above (2) is dissolved in tetrahydrofuran (40 ml), and thereto is added a solution of L-prolinol (1.50 g) and triethylamine (1.60 g) in tetrahydrofuran (10 ml) at room temperature. The mixture is stirred overnight, and the reaction mixture is diluted with ethyl acetate, and washed with aqueous sodium hydrogen carbonate solution and brine. The organic layer is dried over anhydrous sodium sulfate, and the solvent is evaporated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform) and crystallized from a mixture of ether and n-hexane to give (S)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine (4.72 g), m.p. 88–90° C., MS (m/z): 421 ($MH^+$).

(4) A mixture of the compound (3.4 g) obtained in the above (3), a 10% aqueous sodium hydroxide solution (23 ml), and dimethylsulfoxide (34 ml) is stirred at room temperature for 15 hours. The reaction mixture is poured into a 10% aqueous citric acid solution, and the precipitates are crystallized from a mixture of tetrahydrofuran and ether to give (S)-4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine (2.52 g), m.p. 205–208° C., MS (m/z): 391 $(M-H)^-$.

(5) A mixture of the compound (600 mg) obtained in the above (4), 2-aminomethylpyrimidine (217 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (323 mg), 1-hydroxybenzotriazole monohydrate (227 mg) and N,N-dimethylformamide (12 ml) is stirred at room temperature for 8 hours, and the reaction mixture is poured into aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, washed with brine, and dried over anhydrous sodium sulfate. The solvent is evaporated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; chloroform:methanol=50:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidylmethyl) carbamoyl]pyrimidine (610 mg), m.p. 160–163° C.

EXAMPLE 2

(1) To a suspension of lithium aluminum hydride (4.15 g) in tetrahydrofuran (150 ml) is added a solution of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (38.32 g) in tetrahydrofuran (100 ml) under ice-cooling at 5° C. to 10° C. over a period of one hour. After the addition, the ice bath is removed, and the reaction mixture is stirred at room temperature for one hour. To the reaction mixture is added water (4.15 ml) under ice-cooling, and thereto is further added 3N aqueous sodium hydroxide solution (4.15 ml). To the mixture is added water (4.15 ml) three times, and the mixture is stirred at room temperature for one hour. The reaction mixture is treated with magnesium sulfate, and the solid precipitates obtained are filtered. The precipitates are washed with tetrahydrofuran. The filtrate and the washings are combined, and concentrated under reduced pressure, and triturated with a mixture of ethyl acetate and isopropyl ether. The resulting crystals are collected by filtration, and washed well with isopropyl ether to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-hydroxymethylpyrimidine as pale yellow crystalline powder.

First production: yield; 25.10 g, m.p. 162–163° C.

Second production: yield; 2.32 g, m.p. 159–160° C.

In addition, the above solid precipitates are washed again with isopropyl ether, and the filtrate is concentrated under reduced pressure to give colorless crystals. The resulting solid is suspended in isopropyl ether, filtered, and the precipitates are washed well with isopropyl ether and hexane to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-hydroxymethylpyrimidine (4.26 g) as colorless crystals, m.p. 161–162° C.

(2) To a suspension of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-hydroxymethylpyrimidine (25.10 g) obtained in the above (1) in chloroform (150 ml) is added manganese dioxide powder (37.6 g), and the mixture is vigorously stirred at room temperature for one day. To the mixture is further added manganese dioxide powder (12.6 g, 0.5 time amount of the starting compound), and the mixture is stirred for three days. The insoluble materials are quickly removed by filtration on celite, and the filtrate is concentrated under reduced pressure. The residue is suspended in a mixture of ethyl acetate and isopropyl ether. The precipitates are filtered, and washed successively with isopropyl ether and hexane to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (22.43 g) as colorless crystals, m.p. 124–125° C.

(3) A solution of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (2.057 g) in chloroform (20 ml) is treated with m-chloroperbenzoic acid (80%, 1.468 g) at 0° C. for 30 minutes. To the reaction mixture are is added L-prolinol (0.901 g), and then triethylamine (1.33 ml), and the mixture is reacted at 0° C. for one hour. The reaction mixture is warmed to room temperature, and diluted with ethyl acetate. The mixture is washed successively with a saturated aqueous sodium hydrogen carbonate solution, water and a saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The precipitates are removed by filtration through a silica plug. The filtrate is concentrated under reduced pressure to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (1.9990 g) as colorless amorphous, MS (m/z): 377 ($MH^+$).

(4) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (91.0 mg) in tetrahydrofuran (20 ml) is added 1.10 M solution of methyl lithium in ether (1.1 ml) at −78° C., and the mixture is reacted for 10 minutes, and thereto is added aqueous sodium hydrogen carbonate solution. The reaction mixture is extracted with ethyl acetate to give crude (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxyethyl)pyrimidine, MS (m/z): 393 ($MH^+$).

(5) The crude product obtained in the above (4) is treated with manganese dioxide (0.5 g) at room temperature, and the mixture is stirred overnight. The reaction mixture is heated under reflux for 5 hours, and the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and purified by silica gel column chromatography (solvent; chloroform:ethyl acetate=3:1) to give (S)-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-acetylpyrimidine (56.7 mg) as colorless oil, MS (m/z): 391 ($MH^+$).

EXAMPLE 3

(1) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (84 mg) in tetrahydrofuran (about 1 ml) is added dropwise a 1.0M solution of vinyl magnesium bromide in tetrahydrofuran in a dry ice-acetone bath. The reaction mixture is stirred at −78° C. for 10 minutes, and stirred at room temperature for 10 minutes. The reaction mixture is poured into a mixture of ice and a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The organic layer is washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

The obtained crude product is subjected to preparative thin layer chromatography (solvent; ethyl acetate:methanol=20:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxy-2-propen-1-yl)pyrimidine (30 mg) as colorless oil, MS (m/z): 405 ($MH^+$).

(2) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxy-2-propen-1-yl)pyrimidine (144 mg) in chloroform (2.5 ml) is added manganese dioxide (432 mg), and the mixture is vigorously stirred at room temperature for three days. The insoluble materials are removed by filtration on celite, and the filtrate is concentrated under reduced pressure to give pale yellow oil (124 mg). The resulting crude product is purified by silica gel column chromatography (silica gel 20 g, solvent; chloroform:ethyl acetate=2:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(acryloyl)pyrimidine (90 mg) as colorless crystals, m.p. 113–115° C., MS (m/z): 403 ($MH^+$).

(3) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(acryloyl) pyrimidine (72 mg) in ethanol (2 ml) is added morpholine (78 μl) at room temperature, and the mixture is stirred at room temperature for 40 minutes. The reaction mixture is concentrated under reduced pressure, and the residue is poured into water, and the mixture is extracted with ethyl acetate. The organic layer is washed successively with water and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness under reduced pressure to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl) carbonyl]-pyrimidine (91 mg).

The obtained crude product is dissolved in ethyl acetate (10 ml), and the solution is treated with a saturated solution

of hydrochloric acid in methanol (5 ml), and concentrated under reduced pressure. To the residue is added ethyl acetate, and the mixture is filtered. The resulting solid is washed well with hexane to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl)carbonyl]pyrimidine dihydrochloride (65 mg), MS (m/z): 490 ($MH^+$).

EXAMPLE 4

(1) To a solution of 4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-methylthiopyrimidine (972 mg) obtained in the above Example 1-(1) in chloroform (8 ml) is added a solution of m-chloroperbenzoic acid (80%, 598 mg) in chloroform (10 ml) under ice-cooling over a period of 30 minutes. The reaction mixture is stirred under ice-cooling for one hour. The reaction mixture is diluted with a saturated aqueous sodium hydrogen carbonate solution, and the chloroform layer is collected, washed successively with a saturated aqueous sodium hydrogen carbonate solution, water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to quantitatively give 2-methylsulfinyl-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine as colorless caramels, MS (m/z): 384 ($MH^+$).

(2) To a solution of 2-methylsulfinyl-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (whole amount) obtained in the above (1) in tetrahydrofuran (6 ml) is added dropwise a 2N aqueous sodium hydroxide solution (1.32 ml) under ice-cooling over a period of 2 minutes. The reaction mixture is stirred under ice-cooling for 30 minutes, and thereto are added tetrahydrofuran (8 ml) and N,N-dimethylacetamide (6 ml). The reaction mixture is stirred under ice-cooling for 30 minutes, and thereto are added water (5 ml) and N,N-dimethylacetamide (2 ml), and stirred under ice-cooling for one hour. The reaction mixture is acidified with a 10% aqueous citric acid solution, diluted with water, and extracted twice with ethyl acetate. The extracts are combined, washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is separated by silica gel column chromatography (silica gel: 20 g, solvent; chloroform: ethyl acetate=5:1→chloroform:isopropanol=30:1) to give 2-hydroxy-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (618 mg) as slightly yellow crystalline powder, m.p. 195–197° C.

(3) A mixture of 2-hydroxy-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (500 mg) obtained in the above (2), diethylaminobenzene (2 ml) and phosphorus oxychloride (4 ml) is stirred at 80° C. for 30 minutes, and stirred at 100° C. for 5 hours. After cooling, the reaction solution is poured into ice-water, and the mixture is stirred at room temperature for 30 minutes. The resulting mixture is extracted with ethyl acetate, and the organic layer is washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (silica gel: 7 g, solvent; chloroform) to give 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (375 mg) as slightly yellow crystalline powder, m.p. 114–115°, MS (m/z): 356 ($MH^+$).

(4) A mixture of 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (285 mg) obtained in the above (3), 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (197 mg), triethylamine (0.22 ml) and chloroform (3 ml) is stirred at room temperature for 2.5 hours, and stirred at 60° C. for 2.5 hours. The reaction mixture is diluted with ethyl acetate, and washed with water. The aqueous layer is extracted with ethyl acetate, and the organic layer is washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (silica gel: 10 g, solvent; chloroform:methanol=50:1), and concentrated under reduced pressure. The resultant is triturated with isopropyl ether to give 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (290 mg) as colorless crystalline powder, m.p. 179–182° C., MS (m/z): 443 ($MH^+$).

(5) A suspension of 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (290 mg) obtained in the above (4) and 2N aqueous sodium hydroxide solution (1.64 ml) in a mixture of dimethylsulfoxide (5 ml) and water (1 ml) is stirred at room temperature for one hour. To the mixture is added tetrahydrofuran (5 ml), and the mixture is stirred at room temperature for 13 hours. Tetrahydrofuran is evaporated under reduced pressure, and the resulting solution is diluted with water, and neutralized with a 10% aqueous citric acid solution. The precipitates are collected by filtration, washed with water, methanol and isopropyl ether to give 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine (187 mg) as colorless crystalline powder, m.p. 223–226° C. (decomposed), MS (m/z): 413 $(M-H)^-$.

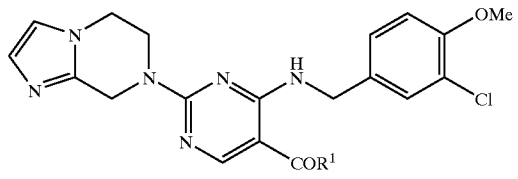
(6) A mixture of 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine (60 mg), 4-methyl-2-aminomethylmorpholine (22.7 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30.6 mg), 1-hydroxybenzotriazole (21.6 mg) and N,N-dimethylformamide (3 ml) is stirred at room temperature for 22 hours. Water is poured into the reaction mixture, and the mixture is extracted with ethyl acetate. The organic layer is washed successively with water, a saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the colorless crystals (70.0 mg), which are further recrystallized from a mixture of chloroform and hexane to give 2-(5,6,7,8-tetrahydroimidazo[1,2-a]-pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(4-methyl-2-morpholinyl)methyl]carbamoyl]pyrimidine (51.7 mg) as colorless needles, m.p. 132–134° C., MS (m/z): 527 ($MH^+$).

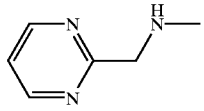
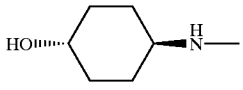
EXAMPLES 5–6

The corresponding starting materials are treated in a similar manner as in Example 4-(6) to give the compounds as listed in the following Table 1.

2.

TABLE 1

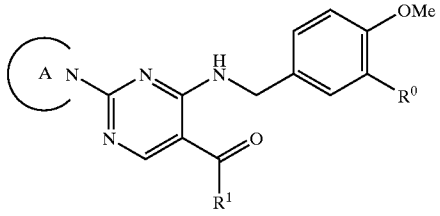


| Ex. No. | $R^1$ | Physiochemical properties |
|---|---|---|
| 5 |  | Powder<br>MS(m/z):506 ($MH^+$) |
| 6 |  | Powder<br>MS(m/z):512 ($MH^+$) |

EXAMPLE 7–21

The corresponding starting materials are treated in a similar give the compounds as listed in the following Table

TABLE 2



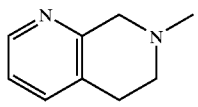
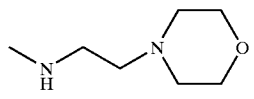
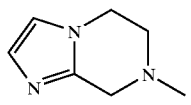
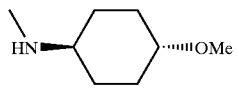
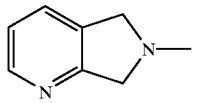
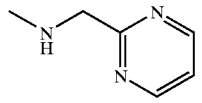
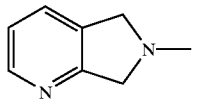
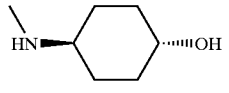
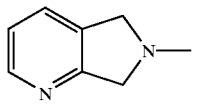
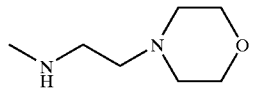
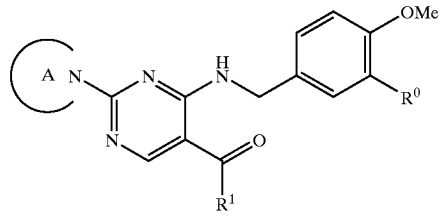
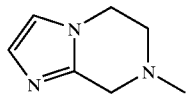
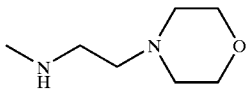
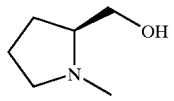
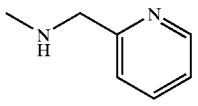
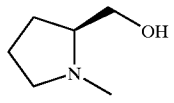
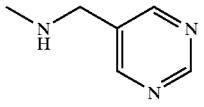
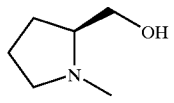
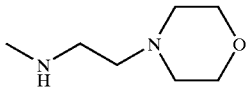
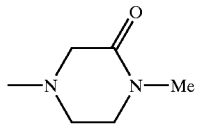
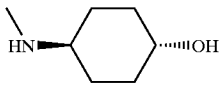
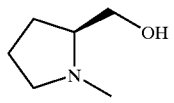
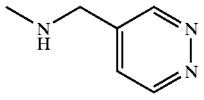
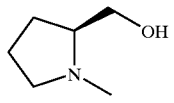
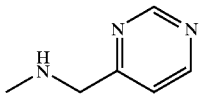
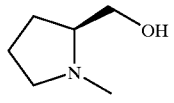
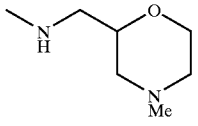
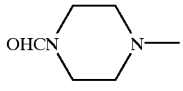
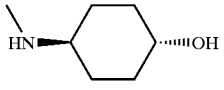
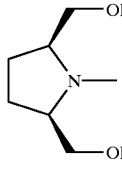
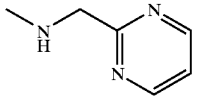
| Ex. No. |  | $R^0$ | $R^1$ | Physiochemical properties |
|---|---|---|---|---|
| 7 |  | Cl |  | Amorphous<br>MS(m/z):538 ($MH^+$) |
| 8 |  | Cl |  | Amorphous<br>MS(m/z):526 ($MH^+$) |
| 9 |  | CN |  | M.p. 243–245° C. |
| 10 |  | CN |  | Amorphous<br>MS(m/z):500 ($MH^+$) |
| 11 |  | CN |  | M.p. 129–132° C. |

TABLE 2-continued



| Ex. No. | A N— | $R^0$ | $R^1$ | Physiochemical properties |
|---|---|---|---|---|
| 12 |  | Cl |  | M.p. 150–152° C. |
| 13 |  | Cl |  | Powder (HCl) MS(m/z):483 ($MH^+$) |
| 14 |  | Cl |  | Amorphous MS(m/z):484 ($MH^+$) |
| 15 |  | Cl |  | Caramel MS(m/z):505 ($MH^+$) |
| 16 |  | Cl |  | Amorphous MS(m/z):503 ($MH^+$) |
| 17 |  | Cl |  | Amorphous MS(m/z):484 ($MH^+$) |
| 18 |  | Cl |  | Amorphous MS(m/z):484 ($MH^+$) |
| 19 |  | Cl |  | Amorphous MS(m/z):505 ($MH^+$) |
| 20 |  | Cl |  | Foam MS(m/z):503 ($MH^+$) |
| 21 |  | Cl |  | Amorphous MS(m/z):514 ($MH^+$) |

EXAMPLE 22

To a solution of diisopropylamine (0.78 g) in tetrahydrofuran (40 ml) is added dropwise a 1.6M solution of n-butyl lithium in hexane (4.82 ml) in a dry ice-acetone bath over a period of 3 minutes. The mixture is stirred in the same bath for 30 minutes. To the mixture is added dropwise a solution of 2,6-dichloropyrazine (0.50 g) in tetrahydrofuran (5 ml) at the same temperature over a period of 15 minutes, and the mixture is stirred for one hour. The reaction mixture is poured into dry ice, and the mixture is stirred at room temperature for one hour. The reaction mixture is diluted with a 10% aqueous hydrochloric acid solution in order to adjust the pH value thereof to about 2, and then extracted with ethyl acetate. The combined organic layers are extracted with a saturated aqueous sodium hydrogen carbonate solution, and the aqueous extract is washed with ethyl acetate, acidified with a 10% aqueous hydrochloric acid, and extracted with ethyl acetate. The combined organic layer is washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is triturated with a mixture of chloroform and hexane (1:1) to give 2-carboxy-3,5-dichloropyrazine (234 mg) as a slightly brown crystalline powder, m.p. 139–141° C., MS (m/z): 191 $(M-H)^-$.

(2) A mixture of 2-carboxy-3,5-dichloropyrazine (226 mg) obtained in the above (1), sodium hydrogen carbonate (118 mg), methyl iodide (0.5 ml) and N,N-dimethylformamide (1.8 ml) is stirred at room temperature for 14 hours. The mixture is diluted with a 10% aqueous citric acid solution, and extracted with ethyl acetate. The combined organic layer is washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 2-methoxycarbonyl-3,5-dichloropyrazine (245 mg) as pale brown crystalline powder, m.p. 60–63° C., MS (m/z): 206 $(M^+)$.

(3) A mixture of 2-methoxycarbonyl-3,5-dichloropyrazine (234 mg) obtained in the above (2), 3-chloro-4-methoxybenzylamine (204 mg), triethylamine (0.17 ml) and dry toluene (3 ml) is stirred at room temperature for 7 hours. The reaction mixture is diluted with a 10% aqueous citric acid solution, and extracted with ethyl acetate. The extract is washed with water and a saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated under reduced pressure. The residue is separated and purified by silica gel column chromatography (silica gel: 5 g, solvent; hexane:chloroform=1:1), and the desired fractions are concentrated under reduced pressure to give 2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-chloropyrazine (102 mg) as pale yellow crystalline powder, m.p. 149–151° C., MS (m/z): 342 $(MH^+)$.

(4) A mixture of 2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-chloropyrazine (150 mg), 2-hydroxymethylpyrrolidine (88.6 mg), and triethylamine (0.12 ml) in tetrahydrofuran (5 ml) is stirred at room temperature for 4 hours, and the mixture is heated at 50° C. for 2 hours. To the mixture is added 2-hydroxymethylpyrrolidine (44.3 mg), and the mixture is stirred at 50° C. for one hour. After cooling, water is added to the reaction mixture, and the mixture is extracted with ethyl acetate. The extract is washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting yellow oil is purified by silica gel column chromatography (solvent; chloroform:hexane=1:1) to give (S)-2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)-pyrazine (123 mg) as pale yellow powder, MS (m/z): 407 $(MH^+)$.

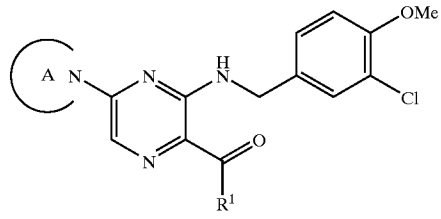
(5) To a solution of (S)-2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (775 mg) obtained in the above (4) in ethanol (8 ml) is added a 4N aqueous sodium hydroxide solution (1.43 ml), and the mixture is stirred at room temperature for 24 hours. The reaction mixture is acidified with 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate. The organic layer is washed with water and brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and washed with diisopropyl alcohol to give (S)-2-carboxy-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (537 mg) as yellow crystals, m.p. 169–171° C., MS (m/z): 391 $(M-H)^-$.

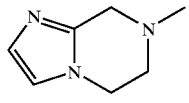
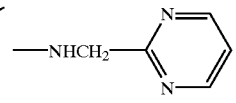
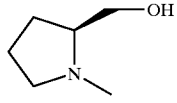
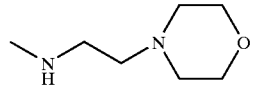
(6) A mixture of (S)-2-carboxy-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (80 mg) obtained in the above (5), 2-aminomethylpyrimidine (26.7 mg), 1,2-dichloroethane (43 mg), 1-hydroxybenzotriazole (30.3 mg) in N,N-dimethylformamide (3 ml) is stirred at room temperature for 18 hours. Water is poured into the reaction mixture, and extracted with ethyl acetate. The extract is washed with water, a saturated aqueous sodium hydrogen carbonate solution, and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; ethyl acetate) to give (S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (87.6 mg), MS (m/z): 484 $(MH^+)$.

EXAMPLES 23–24

The corresponding starting materials are treated in a similar manner as in Example 22 to give the compounds as listed in the following Table 3.

TABLE 3



| Ex. No. | A N— | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 23 |  |  | Amorphous MS(m/z):506 ($MH^+$) |
| 24 |  |  | Amorphous MS(m/z):505 ($MH^+$) |

EXAMPLE 25

A mixture of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(acryloyl)pyrimidine (31 mg), methanol (1 ml) and conc. sulfuric acid (one drop) is heated under reflux for 2 days. After the reaction is complete, the solvent is evaporated under reduced pressure, and the residue is separated by silica gel thin layer chromatography (solvent; chloroform:methanol=30:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl]pyrimidine (27 mg) as colorless oil, MS (m/z): 435 ($MH^+$).

EXAMPLE 26

A solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]-pyrimidine (82.48 g) and benzenesulfonic acid monohydrate (60.06 g) in methanol (1000 ml) is concentrated, and recrystallized from a mixture of methanol and acetone to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)-carbamoyl]pyrimidine dibenzenesulfonate (121.8 g) as colorless crystals, m.p. 158.5–161.5° C.

EXAMPLE 27

A mixture of (S)-4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine (100 mg) obtained in Example 1-(4), 4-amino-1,3,5-trimethylpyrazole (47.9 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (58.7 mg), 1-hydroxybenzotriazole monohydrate (41.3 mg), and N,N-dimethylformamide (3 ml) is stirred at room temperature for 8 hours, and poured into aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, and the organic layer is washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent is evaporated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; chloroform:methanol=5:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine (115 mg), MS (m/z): 500 ($MH^+$).

EXAMPLE 28

(1) A solution of 4-chloro-5-ethoxycarbonyl-2-methylthiopyrimidine (5.0 g) in sulfuryl chloride (20 ml) is heated at 50° C. for one hour. The reaction mixture is concentrated, and thereto is poured a saturated aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, and the organic layer is washed with water and brine, dried over sodium sulfate, and concentrated. The residue is purified by silica gel flash column chromatography (solvent; ethyl acetate=hexane=1:10) to quantitatively give 2,4-dichloro-5-ethoxycarbonylpyrimidine (4.87 g) as yellow oil, MS (m/z): 220 ($M^+$).

(2) To a solution of 2,4-dichloro-5-ethoxycarbonylpyrimidine (4.2 g) obtained in the above (1) and mercaptobenzene (2.30 g) in toluene (40 ml) is added potassium carbonate (3.94 g) at 0° C., and the mixture is stirred at room temperature for one hour, stirred at 50° C. for one hour, and further stirred at 100° C. for 10 minutes. To the mixture is poured water, and the mixture is extracted with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and concentrated. The residue is purified by silica gel flash column chromatography (solvent; ethyl acetate:hexane=1:20→ethyl acetate:hexane=1:10) to give 2-chloro-4-phenylthio-5-ethoxycarbonylpyrimidine (4.16 g) as colorless crystals, MS (m/z): 295 ($MH^+$).

(3) To a solution of 2-chloro-4-phenylthio-5-ethoxycarbonylpyrimidine (4.05 g) obtained in the above (2) in tetrahydrofuran (40 ml) are added L-prolinol (1.66

g) and triethylamine (2.77 g), and the mixture is stirred at room temperature for 20 hours. Water is poured into the reaction mixture, and the mixture is extracted with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel flash column chromatography (solvent; ethyl acetate:hexane=1:2) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-ethoxycarbonylpyrimidine (4.16 g) as colorless viscous oil, MS (m/z): 360 ($MH^+$).

(4) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-ethoxycarbonylpyrimidine (4.10 g) obtained in the above (3) in ethanol (50 ml) is added a 4N aqueous sodium hydroxide solution (8.6 ml), and the mixture is stirred at room temperature for 15 hours. To the reaction solution is added a 10% aqueous citric acid solution (30 ml) until the solution becomes weak acidic, and the mixture is extracted with ethyl acetate. The organic layer is washed with water and brine, dried over sodium sulfate, and concentrated to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-carboxypyrimidine (3.65 g) as colorless crystals, MS (m/z): 330 $(M-H)^-$.

(5) A mixture of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-carboxypyrimidine (2.55 g) obtained in the above (4), 2-aminomethylpyrimidine (1.09 g), 1,2-dichloroethane (1.77 g) and 1-hydroxybenzotriazole (1.25 g) in N,N-dimethylformamide (40 ml) is stirred at room temperature for 16 hours. To the mixture is poured water, and the mixture is extracted with ethyl acetate. The organic layer is washed with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and concentrated to give pale yellow crystals (4.05 g), which is further purified by silica gel flash column chromatography (solvent; ethyl acetate) to give 2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-[N-(2-pyrimidylmethyl)carbamoyl]pyrimidine (2.39 g) as colorless crystals, m.p., 154–156° C., IR (Nujol): 1633 $cm^{-1}$, MS (m/z): 423 ($MH^+$).

(6) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-[N-(2-pyrimidylmethyl)carbamoyl] pyrimidine (100 mg) obtained in the above (5) in chloroform (3 ml) is added m-chloroperbenzoic acid (70.1 mg) at 0° C., and the mixture is stirred at 0° C. for 30 minutes. To the mixture are added 3-chlorobenzylamine (50.3 mg) and triethylamine (48.0 mg) at 0° C., and the mixture is stirred at room temperature for 17 hours. To the mixture is poured water, and the mixture is extracted with chloroform. The organic layer is washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to give yellow oil (169 mg), which is purified by silica gel flash column chromatography (solvent; ethyl acetate), and triturated with a mixture of ethyl acetate and hexane to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chlorobenzylamino)-5-[N-(2-pyrimidylmethyl)-carbamoyl]pyrimidine (95.3 mg) as colorless powder, m.p. 153–156° C., IR (Nujol): 3241, 1637 $cm^{-1}$, MS (m/z): 454 ($MH^+$).

(7) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-[N-(2-pyrimidylmethyl)carbamoyl] pyrimidine (100 mg) obtained in the above (5) in chloroform (3 ml) is added m-chloroperbenzoic acid (70%, 70.1 mg) at 0° C., and the mixture is stirred at 0° C. for 30 minutes. To the mixture are added 4-methoxybenzylamine (48.8 mg) and triethylamine (48.0 mg) at 0° C., and the mixture is stirred at room temperature for 20 minutes. To the mixture is poured water, and the mixture is extracted with chloroform, and the organic layer is washed with brine, dried over sodium sulfate, and concentrated to give a yellow oil (143 mg), which is purified by silica gel flash column chromatography (solvent; ethyl acetate) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(4-methoxybenzylamino)-5-[N-(2-pyrimidylmethyl)-carbamoyl]pyrimidine (88.2 mg) as colorless powder, IR (Neat): 3296, 1633 $cm^{-1}$, MS (m/z): 450 ($MH^+$).

## EXAMPLE 29

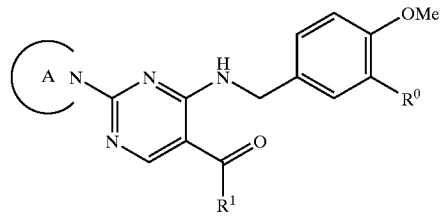
(1) A solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (10.0 mg) in tetrahydrofuran (1.0 ml) obtained in Example 2 (3) is treated with a 1.6M solution of n-butyl lithium in hexane (83 $\mu$l) at −78° C. for 3 minutes, and thereto is added an aqueous sodium hydrogen carbonate solution. The reaction mixture is extracted with ethyl acetate to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxypentyl) pyrimidine (13.7 mg) as oil.

(2) (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxypentyl)pyrimidine obtained in the above is treated with manganese dioxide (25 mg) at room temperature, and thereto is added gradually additional manganese dioxide (100 mg), and the mixture is stirred overnight. The reaction mixture is heated under reflux for 5 hours, and the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and separated with preparative thin layer chromatography to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-pentanoylpyrimidine (5.8 mg) as colorless oil, MS (m/z): 433 ($MH^+$).

## EXAMPLES 30–83

The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the following Table 4.

TABLE 4



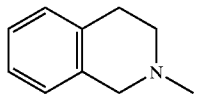
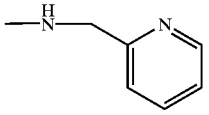
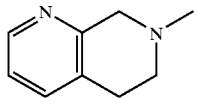
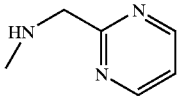
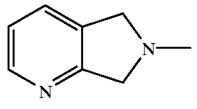
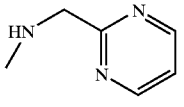
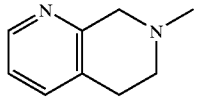
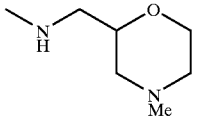
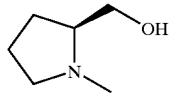
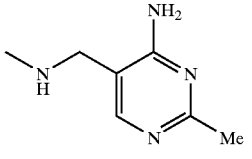
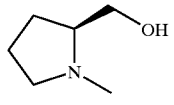
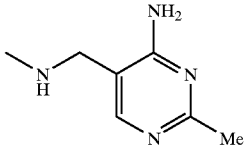
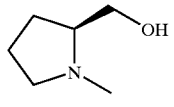
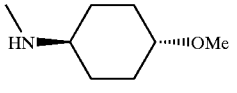
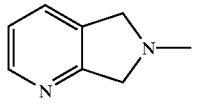
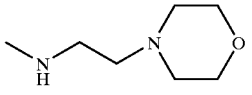
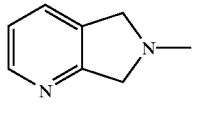
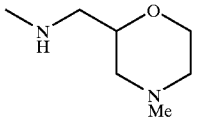
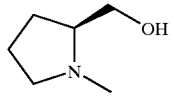
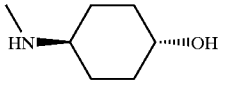
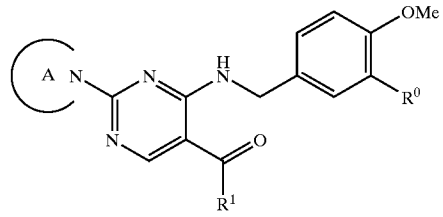
| Ex. No. | A N— | $R^0$ | $R^1$ | Physiochemical properties |
|---|---|---|---|---|
| 30 |  | Cl |  | M.p. 210–214° C. |
| 31 |  | Cl |  | Amorphous MS(m/z):517 ($MH^+$) |
| 32 |  | Cl |  | Amorphous MS(m/z):503 ($MH^+$) |
| 33 |  | Cl |  | Amorphous MS(m/z):538 ($MH^+$) |
| 34 |  | Cl |  | HCl salt M.p. 223–226° C. |
| 35 |  | Cl |  | Amorphous MS(m/z):513 ($MH^+$) |
| 36 |  | Cl |  | Amorphous MS(m/z):504 ($MH^+$) |
| 37 |  | Cl |  | MS(m/z):524 ($MH^+$) |
| 38 |  | Cl |  | Amorphous MS(m/z):524 ($MH^+$) |
| 39 |  | Cl |  | Foam MS(m/z):490 ($MH^+$) |

TABLE 4-continued



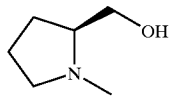
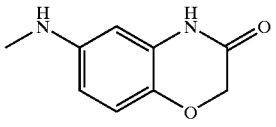
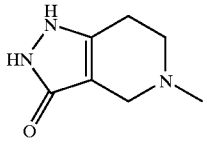
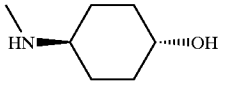
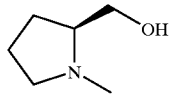
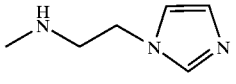
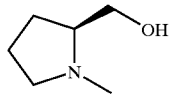
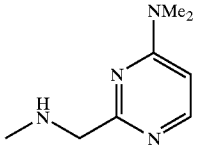
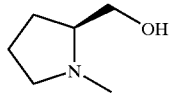
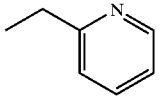
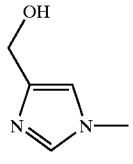
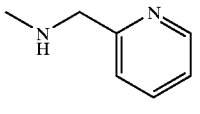
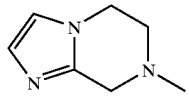
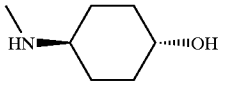
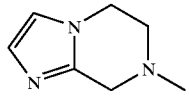
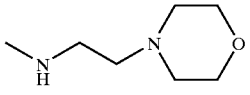
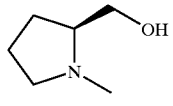
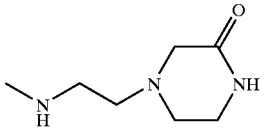
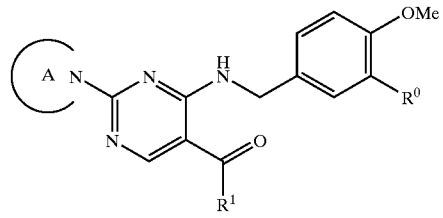
| Ex. No. | A N— | $R^0$ | $R^1$ | Physiochemical properties |
|---|---|---|---|---|
| 40 |  | Cl |  | Amorphous MS(m/z):539 ($MH^+$) |
| 41 |  | Cl |  | Amorphous MS(m/z):528 ($MH^+$) |
| 42 |  | Cl |  | Amorphous MS(m/z):500 ($MH^+$) |
| 43 |  | Cl |  | Amorphous MS(m/z):527 ($MH^+$) |
| 44 |  | Cl |  | Amorphous MS(m/z):468 ($MH^+$) |
| 45 |  | Cl |  | M.p. 220–222° C. |
| 46 |  | $NO_2$ |  | Amorphous MS(m/z):523 ($MH^+$) |
| 47 |  | $NO_2$ |  | M.p. 188–190° C. |
| 48 |  | Cl |  | Amorphous MS(m/z):518 ($MH^+$) |

TABLE 4-continued



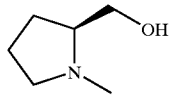
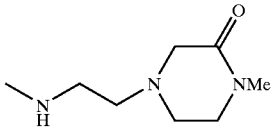
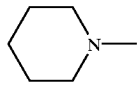
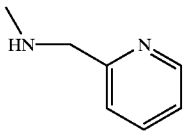
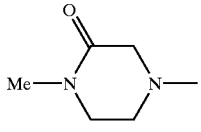
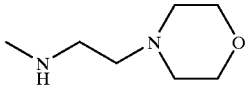
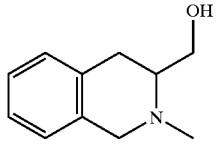
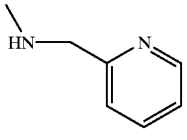
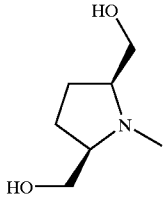
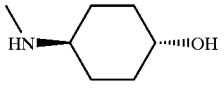
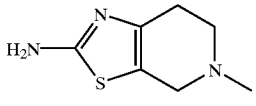
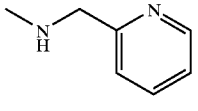
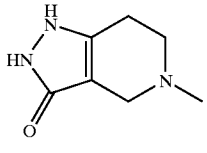
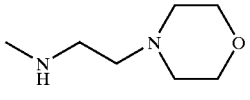
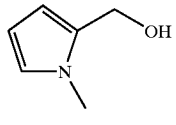
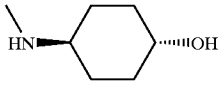
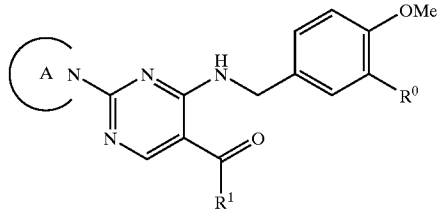
| Ex. No. | A N— | $R^0$ | $R^1$ | Physiochemical properties |
|---|---|---|---|---|
| 49 |  | Cl |  | Amorphous MS(m/z):532 ($MH^+$) |
| 50 |  | Cl |  | M.p. 179–183° C. |
| 51 |  | Cl |  | Amorphous MS(m/z):518 ($MH^+$) |
| 52 |  | Cl |  | Powder (HCl) MS(m/z):545 ($MH^+$) |
| 53 |  | Cl |  | Amorphous MS(m/z):520 ($MH^+$) |
| 54 |  | Cl |  | Powder (HCl) MS(m/z):537 ($MH^+$) |
| 55 |  | Cl |  | Amorphous MS(m/z):543 ($MH^+$) |
| 56 |  | Cl |  | M.p. 181–183° C. |

TABLE 4-continued



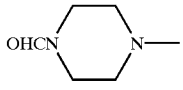
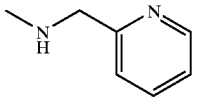
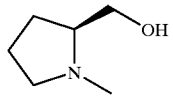
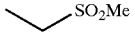
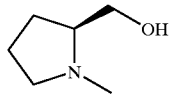
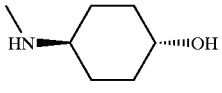
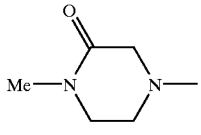
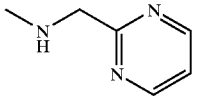
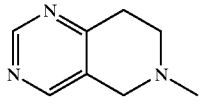
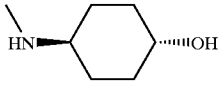
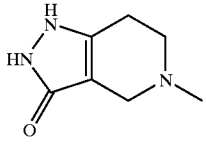
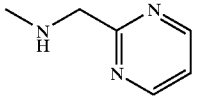
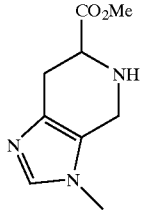
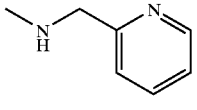
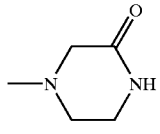
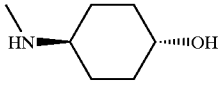
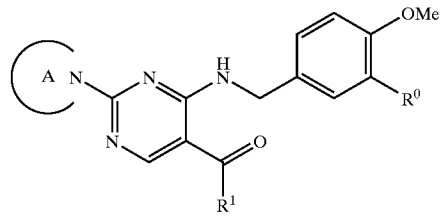
| Ex. No. | A N— | $R^0$ | $R^1$ | Physiochemical properties |
|---|---|---|---|---|
| 57 |  | Cl |  | Powder (HCl) MS(m/z):496 ($MH^+$) |
| 58 |  | Cl |  | M.p. 199–200° C. |
| 59 |  | $NO_2$ |  | M.p. 209.5–211.5° C. |
| 60 |  | Cl |  | M.p. 228–230.5° C. |
| 61 |  | Cl |  | Amorphous MS(m/z):524 ($MH^+$) |
| 62 |  | Cl |  | Amorphous MS(m/z):522 ($MH^+$) |
| 63 |  | Cl |  | Amorphous MS(m/z):563 ($MH^+$) |
| 64 |  | Cl |  | Amorphous MS(m/z):489 ($MH^+$) |

TABLE 4-continued



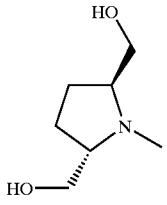
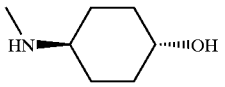
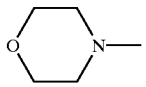
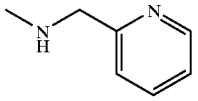
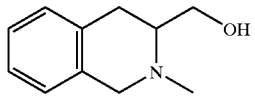
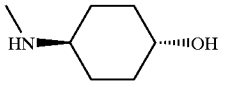
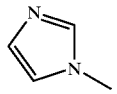
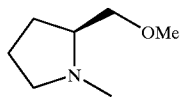
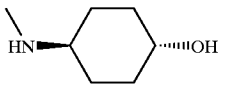
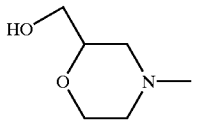
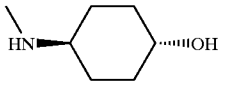
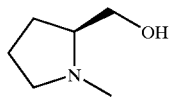
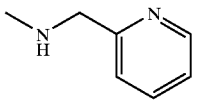
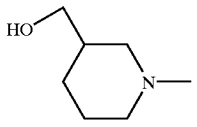
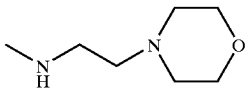
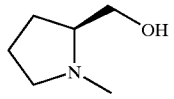
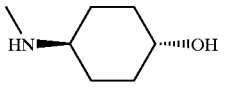
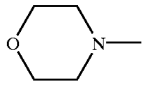
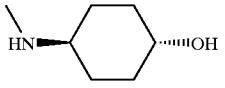
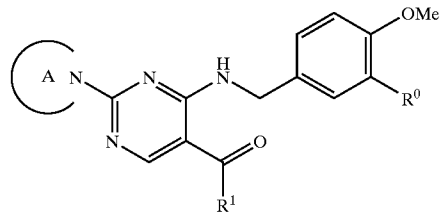
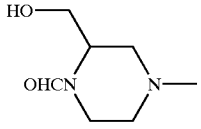
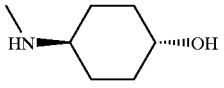
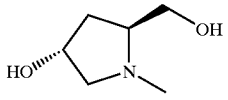
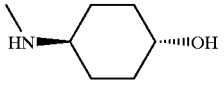
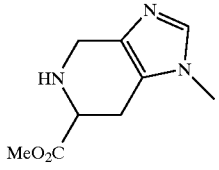
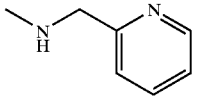
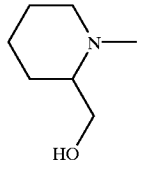
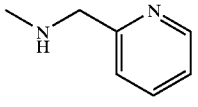
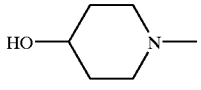
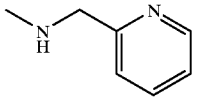
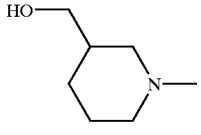
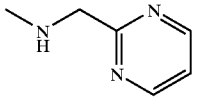
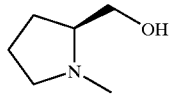
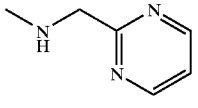
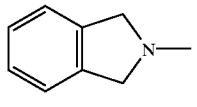
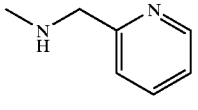
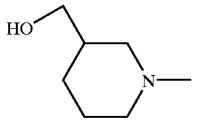
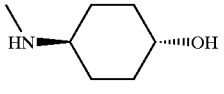
| Ex. No. | A N— | $R^0$ | $R^1$ | Physiochemical properties |
|---|---|---|---|---|
| 65 |  | Cl |  | Amorphous MS(m/z):520 ($MH^+$) |
| 66 |  | Cl |  | M.p. 176–180° C. |
| 67 |  | CN |  | Powder (HCl) MS(m/z):543 ($MH^+$) |
| 68 |  | Cl |  | M.p. 143–145° C. |
| 69 |  | Cl |  | Powder (HCl) MS(m/z):504 ($MH^+$) |
| 70 |  | Cl |  | M.p. 130° C. |
| 71 |  | CN |  | Powder (HCl) MS(m/z):474 ($MH^+$) |
| 72 |  | Cl |  | Amorphous MS(m/z):519 ($MH^+$) |
| 73 |  | CN |  | Powder (HCl) MS(m/z):481 ($MH^+$) |
| 74 |  | Cl |  | M.p. 116–119° C. |

TABLE 4-continued

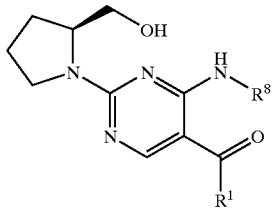


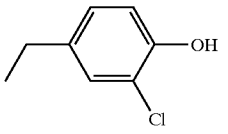
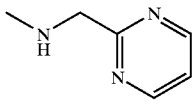
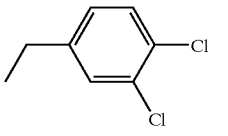
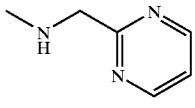
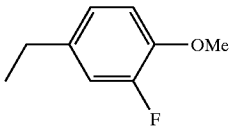
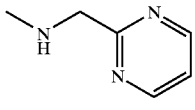
| Ex. No. | A N— | $R^0$ | $R^1$ | Physiochemical properties |
|---|---|---|---|---|
| 75 |  | Cl |  | M.p. 159–161° C. |
| 76 |  | Cl |  | Powder (HCl) MS(m/z):506 ($MH^+$) |
| 77 |  | Cl |  | Amorphous MS(m/z):563 ($MH^+$) |
| 78 |  | Cl |  | Powder (HCl) MS(m/z):497 ($MH^+$) |
| 79 |  | Cl |  | M.p. 210–214° C. |
| 80 |  | Cl |  | M.p. 149–151.5° C. |
| 81 |  | $NO_2$ |  | Amorphous MS(m/z):495 ($MH^+$) |
| 82 |  | Cl |  | M.p. 215° C. |
| 83 |  | Cl |  | M.p. 151–152° C. |

EXAMPLE 84–86

The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the following Table 5.

TABLE 5



| Ex. No. | $R^8$ | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 84 |  |  | Foam MS(m/z):470 ($MH^+$) |
| 85 |  |  | Powder MS(m/z):488 ($MH^+$) |
| 86 |  |  | Powder MS(m/z):468 ($MH^+$) |

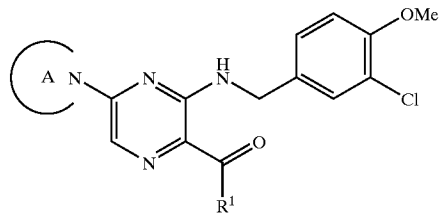
EXAMPLE 87

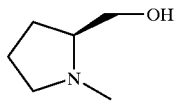
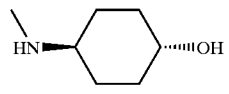
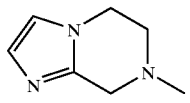
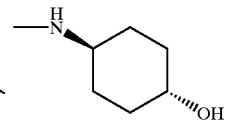
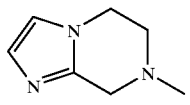
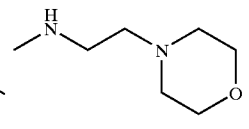
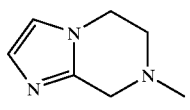
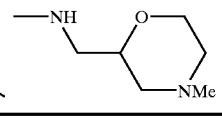
A mixture of (S)-2-carboxy-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl) pyrazine (80 mg) obtained in Example 22 (5), 2-aminomethyl-4-methylmorpholine (31.9 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (43 mg), 1-hydroxybenzotriazole (30.3 mg) in N,N-dimethylformamide (3 ml) is stirred at room temperature for 18 hours. To the reaction mixture is poured water, and the mixture is extracted with ethyl acetate. The extract is washed with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel flash column chromatography (solvent; ethyl acetate) to give (S)-2-[N-(4-methyl-2-morpholinyl) methylcarbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (80.5 mg), MS (m/z): 505 ($MH^+$), IR (Nujol): 3295, 1635 $cm^{-1}$.

EXAMPLES 88–91

The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the following Table 6.

TABLE 6

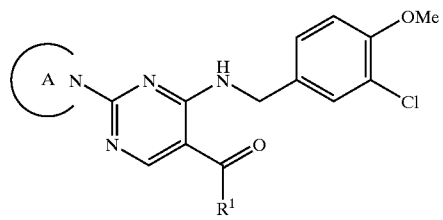


| Ex. No. |  | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 88 |  |  | M.p. 177–179° C, MS(m/z):490 ($MH^+$) |
| 89 |  |  | M.p. 167–169° C. MS(m/z):512 ($MH^+$) |
| 90 |  |  | M.p. 140.5–141.5° C. |
| 91 |  |  | Amorphous MS(m/z):527 ($MH^+$) |

EXAMPLES 92–145

The corresponding starting compounds are treated in a similar give the compounds as listed in the following Table 7.

TABLE 7



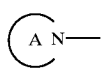
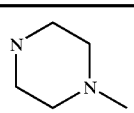
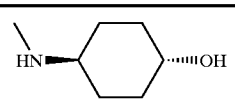
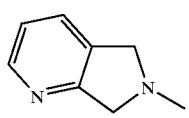
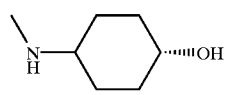
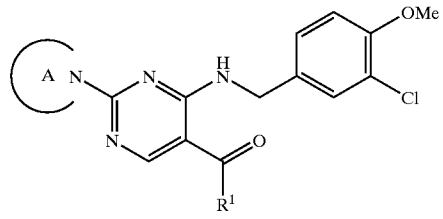
| Ex. No. |  | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 92 |  |  | Powder MS(m/z):475 ($MH^+$) |
| 93 |  |  | Powder MS(m/z):509 ($MH^+$) |

TABLE 7-continued



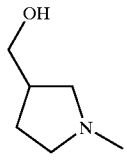
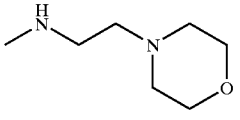
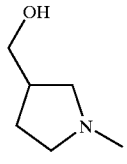
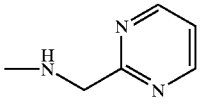
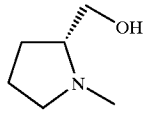
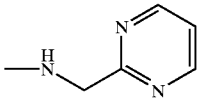
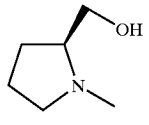
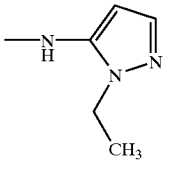
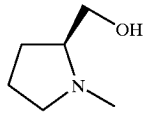
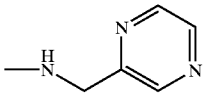
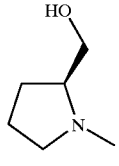
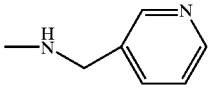
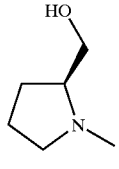
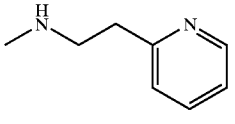
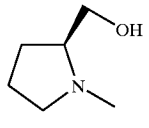
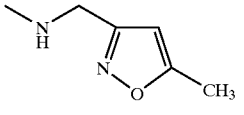
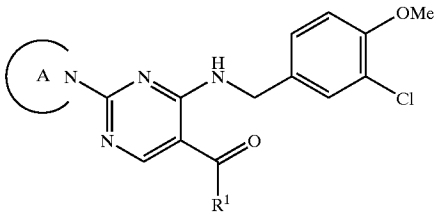
| Ex. No. | A N— | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 94 |  |  | Amorphous MS(m/z):512 ($MH^+$) |
| 95 |  |  | M.p. 150–152° C. |
| 96 |  |  | M.p. 162–163° C. |
| 97 |  |  | Amorphous MS(m/z):486 ($MH^+$) |
| 98 |  |  | Amorphous MS(m/z):484 ($MH^+$) |
| 99 |  |  | Amorphous MS(m/z):483 ($MH^+$) |
| 100 |  |  | Amorphous MS(m/z):497 ($MH^+$) |
| 101 |  |  | M.p. 148–150° C. |

TABLE 7-continued



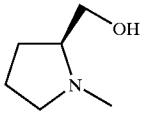
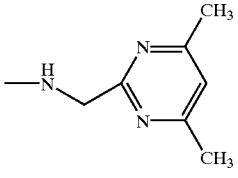
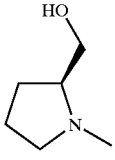
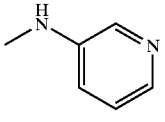
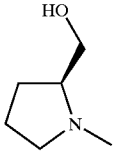
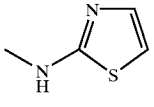
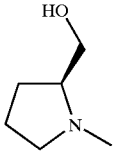
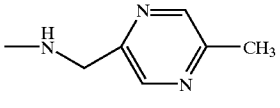
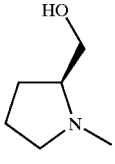
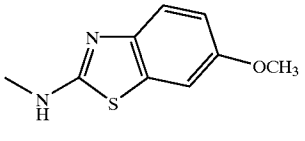
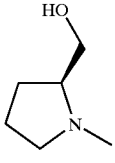
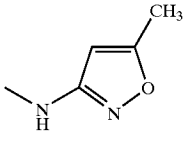
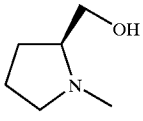
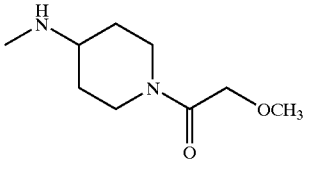
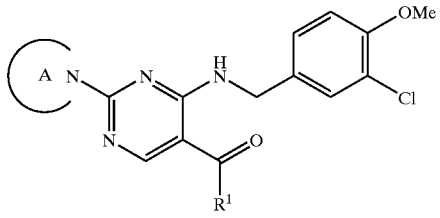
| Ex. No. | A N— | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 102 |  |  | Amorphous MS(m/z):512 ($MH^+$) |
| 103 |  |  | M.p. 210–213° C. |
| 104 |  |  | M.p. 195–198° C. |
| 105 |  |  | Amorphous MS(m/z):498 ($MH^+$) |
| 106 |  |  | M.p. 232–235° C. |
| 107 |  |  | M.p. 207–208° C. |
| 108 |  |  | Amorphous MS(m/z):547 ($MH^+$) |

TABLE 7-continued



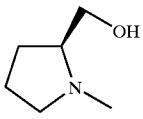
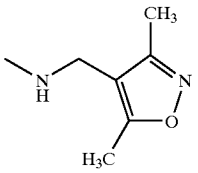
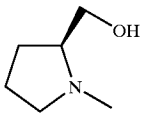
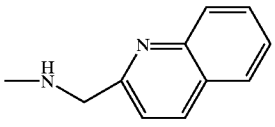
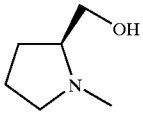
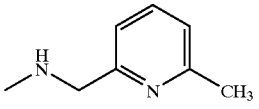
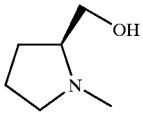
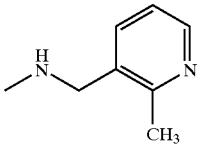
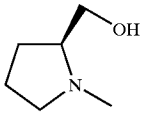
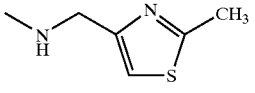
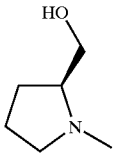
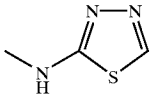
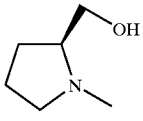
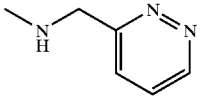
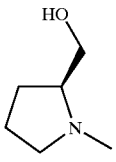
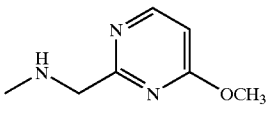
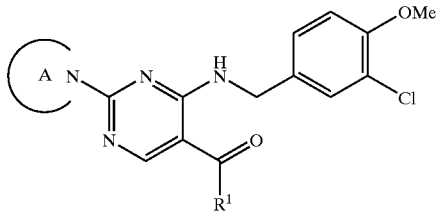
| Ex. No. |  | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 109 |  |  | Amorphous MS(m/z):501 ($MH^+$) |
| 110 |  |  | M.p. 172–173° C. |
| 111 |  |  | M.p. 145–147° C. |
| 112 |  |  | Amorphous MS(m/z):497 ($MH^+$) |
| 113 |  |  | M.p. 148–150° C. |
| 114 |  |  | M.p. 217–219° C. |
| 115 |  |  | Amorphous MS(m/z):484 ($MH^+$) |
| 116 |  |  | Amorphous MS(m/z):514 ($MH^+$) |

TABLE 7-continued



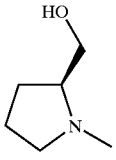
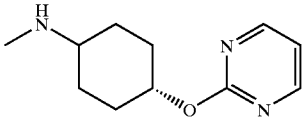
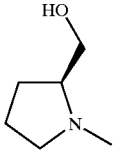
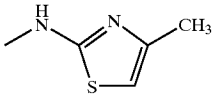
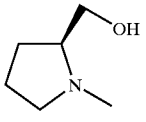
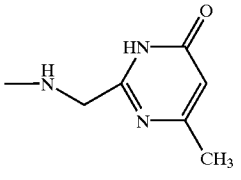
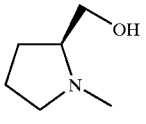
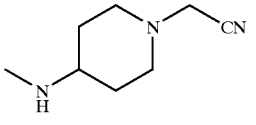
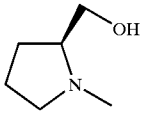
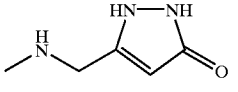
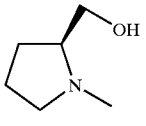
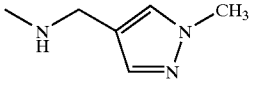
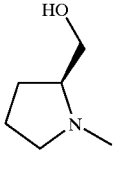
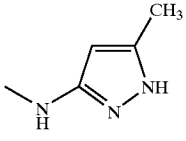
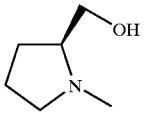
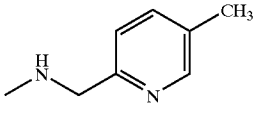
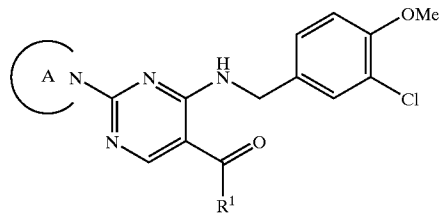
| Ex. No. |  | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 117 |  |  | Amorphous MS(m/z):568 ($MH^+$) |
| 118 |  |  | M.p. 217–220° C. |
| 119 |  |  | M.p. 212–214° C. |
| 120 |  |  | Amorphous MS(m/z):514 ($MH^+$) |
| 121 |  |  | Amorphous MS(m/z):488 ($MH^+$) |
| 122 |  |  | M.p. 142–144° C. |
| 123 |  |  | Amorphous MS(m/z):472 ($MH^+$) |
| 124 |  |  | Amorphous MS(m/z):497 ($MH^+$) |

TABLE 7-continued



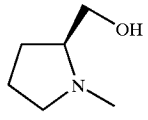
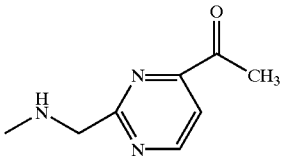
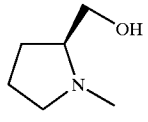
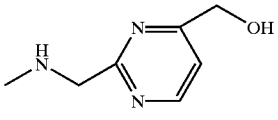
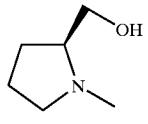
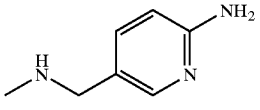
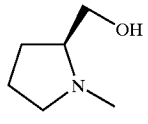
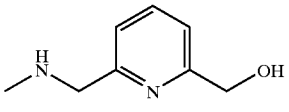
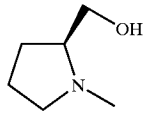
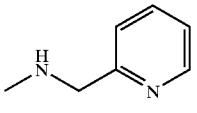
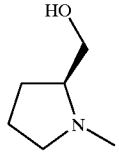
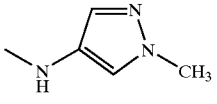
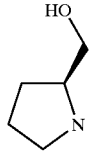
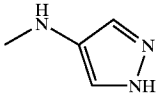
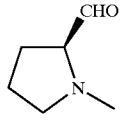
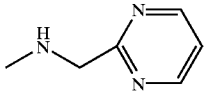
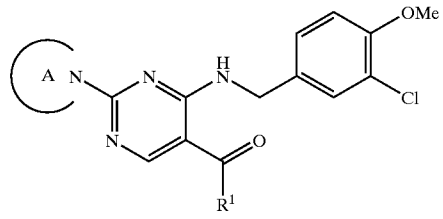
| Ex. No. | A N— | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 125 |  |  | M.p. 143–146° C. |
| 126 |  |  | Amorphous MS(m/z):514 ($MH^+$) |
| 127 |  |  | Amorphous MS(m/z):498 ($MH^+$) |
| 128 |  |  | Amorphous MS(m/z):513 ($MH^+$) |
| 129 |  |  | M.p. 101–103° C. |
| 130 |  |  | M.p. 215–217° C. |
| 131 |  |  | M.p. 180–183° C. |
| 132 |  |  | Oil MS(m/z):482 ($MH^+$) |

TABLE 7-continued



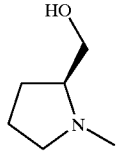
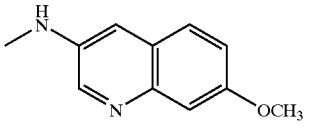
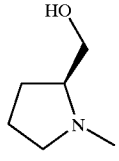
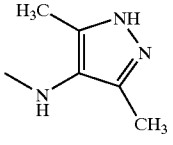
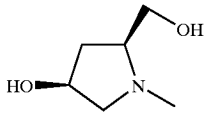
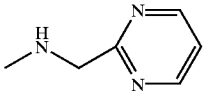
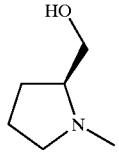
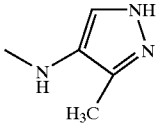
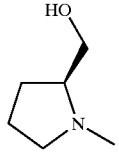
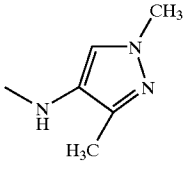
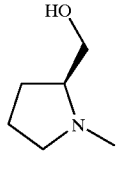
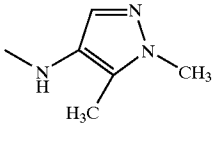
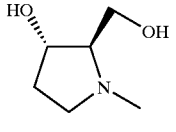
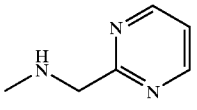
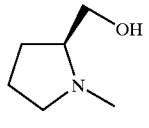
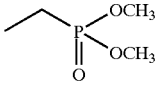
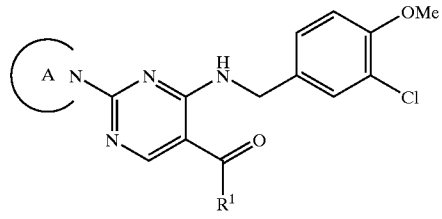
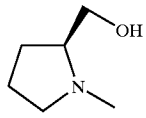
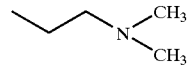
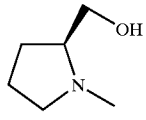
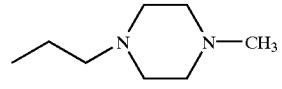
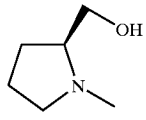
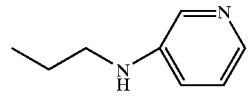
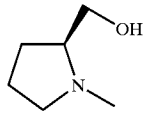
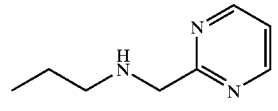
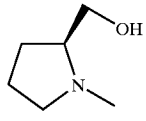
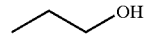
| Ex. No. | A N— | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 133 |  |  | M.p. 176–179° C. |
| 134 |  |  | M.p. 224–227° C. |
| 135 |  |  | Amorphous MS(m/z):500 ($MH^+$) |
| 136 |  |  | M.p. 177–180° C. |
| 137 |  |  | Powder MS(m/z):486 ($MH^+$) |
| 138 |  |  | Powder MS(m/z):486 ($MH^+$) |
| 139 |  |  | Powder MS(m/z):500 ($MH^+$) |
| 140 |  |  | Amorphous MS(m/z):499 ($MH^+$) |

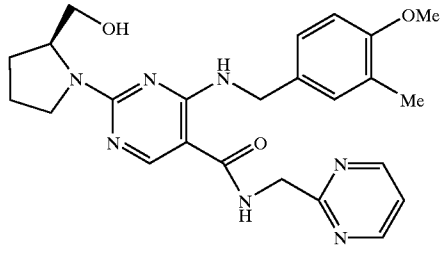
TABLE 7-continued



| Ex. No. | A N— | $R^1$ | Physiochemical properties |
|---|---|---|---|
| 141 |  |  | Amorphous MS(m/z):448 ($MH^+$) |
| 142 |  |  | Amorphous MS(m/z):503 ($MH^+$) |
| 143 |  |  | M.p. 112–114° C. |
| 144 |  |  | Amorphous MS(m/z):512 ($MH^+$) |
| 145 |  |  | M.p. 123–125° C. |

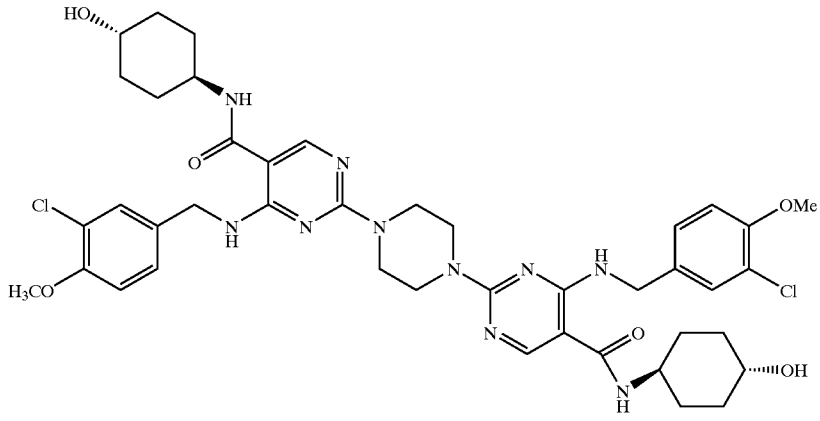
EXAMPLE 146

The corresponding starting compounds are treated in a similar manner to give the compound of the following formula as foam, MS (m/z): 464 ($MH^+$).



EXAMPLE 147

The corresponding starting compounds are treated in a similar manner to give the compound of the following formula, m.p. 140–144° C.



EXAMPLE 148

To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidylmethyl)carbamoyl]-pyrimidine (307 mg) obtained in Example 1-(5) in methylene chloride (6 ml) is added dropwise boron bromide (300 μl) under ice-cooling. The reaction mixture is stirred at 0° C. for 4 hours, and thereto is added methanol, and then a saturated aqueous sodium hydrogen carbonate solution under ice-cooling. The mixture is extracted with a mixture of ethyl acetate and tetrahydrofuran, and the organic layer is washed successively with water and brine. The mixture is dried over sodium sulfate, and concentrated under reduced pressure to give a slightly brown amorphous (227 mg). The resultant is suspended in chloroform, and the resulting insoluble materials are removed by filtration. The filtrate is subjected to silica gel column chromatography, and further purified by NH-silica gel column chromatography to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-hydroxybenzylamino)-5-[N-(2-pyrimidylmethyl) carbamoyl]pyrimidine (129 mg) as a colorless foam, MS (m/z): 470 ($MH^+$), IR (Nujol): 3279, 1632, 1593, 1569, 1518, 1463 $cm^{-1}$.

EXAMPLE 149

(1) A suspension of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (2.00 g) obtained in Example 1 (1) in dimethylsulfoxide (10 ml) is treated with 10% aqueous sodium hydroxide solution (10 ml) at room temperature. To the reaction mixture is added dimethylsulfoxide (5 ml), and the mixture is stirred at room temperature overnight. To the resulting colorless solution is added citric acid until the solution becomes acidic. To the solution is added an excess amount of water (about 50 ml), and the resulting precipitates are collected by filtration. The precipitates are washed with isopropyl alcohol and isopropyl ether successively, and dried under reduced pressure to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine (1.864 g) as pale yellow impalpable powder, m.p. 238–240° C. (dec.).

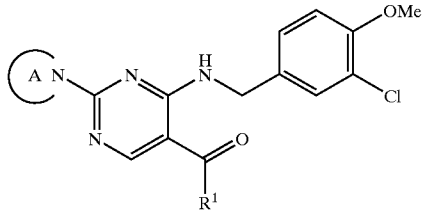
(2) To a suspension of 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2-methylthiopyrimidine (200 mg) in methylene chloride (5 ml) are added oxalyl chloride (150 mg) and N,N-dimethylformamide, and the mixture is stirred at room temperature for 30 minutes, and concentrated. To a suspension of the resulting acid chloride compound and 5-aminopyrimidine (84.0 mg) in methylene chloride (5 ml) is added dimethylaminopyridine (144 mg) at room temperature, and the mixture is stirred at room temperature. To the mixture is poured water, and the mixture is extracted with ethyl acetate. The extract is washed with a saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over sodium sulfate, and concentrated. The residue is triturated with a mixture of ethyl acetate and n-hexane to give 4-(3-chloro-4-methoxybenzylamino)-5-(5-pyrimidinylaminocarbonyl)-2-methylthiopyrimidine (216 mg) as pale yellow needles, m.p. 238–240° C., IR (Nujol): 3251, 1666 $cm^{-1}$, MS (m/z): 416 ($M^+$).

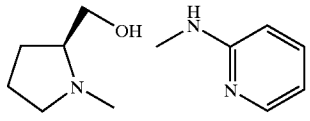
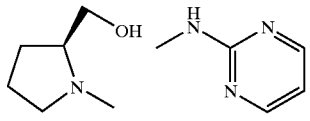
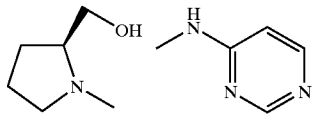
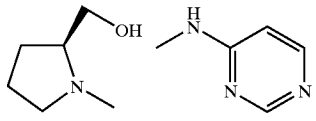
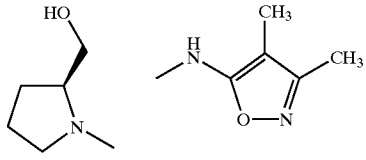
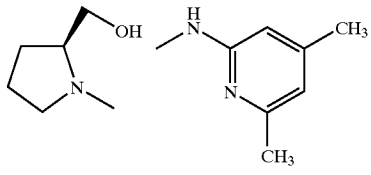
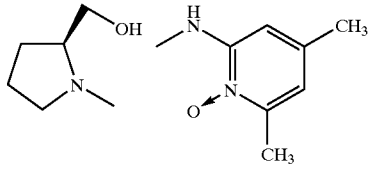
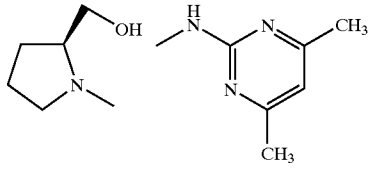
(3) To a suspension of the compound (150 mg) obtained in the above (2) in chloroform (10 ml) is added m-chloroperbenzoic acid (107 mg) at 0° C., and the mixture is stirred at 0° C. for one hour, and stirred at room temperature for one hour. To the mixture is added m-chloroperbenzoic acid (53 mg) at 0° C., and the mixture is stirred at 0° C. for 30 minutes. To the mixture are added L-prolinol (43.7 mg) and triethylamine (72.9 mg) at 0° C., and the mixture is stirred at room temperature for 20 hours. To the mixture is poured water, and the mixture is extracted with chloroform. The organic layer is washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to give yellow viscous oil (201 mg), which is purified by NH-silica gel flash column chromatography (solvent; ethyl acetate), washed with a mixture of ethyl acetate and hexane to give (S)-4-(3-chloro-4-methoxybenzylamino)-5-(5-pyrimidinylaminocarbonyl)-2-(hydroxymethyl-1-pyrrolidinyl)pyrimidine (81 mg) as colorless needles, m.p. 192–195° C., IR (Nujol): 3279, 1669 $cm^{-1}$, MS (m/z): 470 ($MH^+$).

EXAMPLES 150–157

The corresponding starting compounds are treated in a similar manner as in Example 149 to give the compounds as listed in the following Table 8.

TABLE 8



| Ex. No. | A N— | $R^1$ | Physicochemical properties |
|---|---|---|---|
| 150 |  | | Powder MS(m/z):469 (MH+) |
| 151 |  | | Powder MS(m/z):470 (MH+) |
| 152 |  | | M.p. 182–185° C. |
| 153 |  | | M.p. 176–178° C. |
| 154 |  | | Powder MS(m/z):487 (MH+) |
| 155 |  | | M.p. 161–163° C. |
| 156 |  | | Powder MS(m/z):513 (MH+) |
| 157 |  | | Powder MS(m/z):498 (MH+) |

EXAMPLE 158

(1) A suspension of 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2-methylthiopyrimidine (154.0 mg) obtained in Example 149 (1) in methylene chloride (5 ml) is treated with oxalyl chloride (119 μl) at room temperature, and thereto is added N,N-dimethylformamide. The mixture is stirred for one hour, and the solvent is evaporated under reduced pressure. The residue is treated with ether, and kept in a refrigerator overnight. The volatile materials are removed under reduced pressure, and the residue is treated with an excess amount of diazomethane at 0° C. and kept in a refrigerator overnight. The reaction is quenched with methanol, and the mixture is purified by silica gel chromatography (solvent; hexane:ethyl acetate=2:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-(diazomethylcarbonyl)-2-methylthiopyrimidine (21.5 mg) as pale yellow solid, IR (Nujol): 3277, 2115, 1607, 1567, 1461, 1377, 1357, 1141 $cm^{-1}$, MS (m/z): 364 ($MH^+$), m.p. 162–165° C. (dec.).

(2) A suspension of the compound obtained in the above (1) (16.5 mg) in methanol (3 ml) is treated with toluenesulfonic acid monohydrate (16.5 mg) at room temperature. The solvent is evaporated under reduced pressure, and the residue is purified by preparative TLC (solvent; hexane:ethyl acetate=2:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-(methoxymethylcarbonyl)-2-methylthiopyrimidine (11.0 mg) as colorless oil.

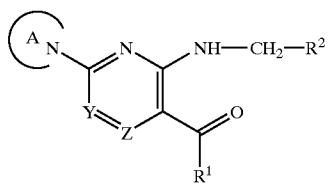
(3) A solution of the compound (11.0 mg) obtained in the above (2) in chloroform (1 ml) is treated with m-chloroperbenzoic acid (7.4 mg) at 0° C. The mixture is treated with triethylamine (8.3 μl) and L-prolinol (36 mg) at room temperature, and the reaction mixture is stirred overnight. The reaction mixture is diluted with ethyl acetate, washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, and dried over sodium sulfate. The residue is purified by preparative TLC (solvent; chloroform:ethyl acetate 1:1) to give (S)-4-(3-chloro-4-methoxybenzylamino)-5-(methoxymethylcarbonyl)-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine (8.5 mg) as colorless oil, MS (m/z): 421 ($MH^+$).

Industrial Applicability

The compound (I) of the present invention and a pharmaceutically acceptable salt thereof exhibit excellent PDE V inhibitory activities, and they are useful pharmaceutical compounds for the prophylaxis or treatment of penile erectile dysfunction, etc.

What is claimed is:

**1**. An aromatic nitrogen-containing 6-membered cyclic compound of the formula (I):



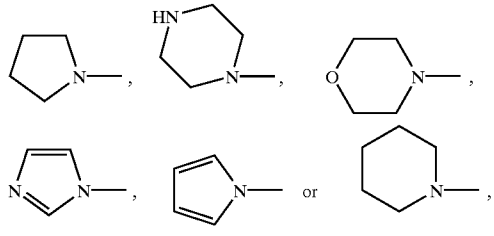
(I)

wherein Ring A is a substituted or unsubstituted nitrogen-containing heterocyclic group; $R^1$ is a substituted or unsubstituted lower alkyl group, a group of the formula: —NH—Q—$R^3$ (in which $R^3$ is a substituted or unsubstituted nitrogen containing heterocyclic group, and Q is a lower alkylene group or a single bond), or a group of the formula: —NH—$R^4$ (in which $R^4$ is a substituted or unsubstituted

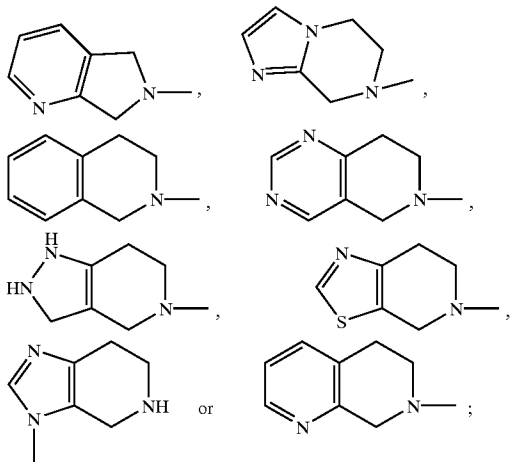
cycloalkyl group); $R^2$ is a substituted or unsubstituted aryl group; Z is a group of the formula: =CH—, and Y is a group of the formula: =N—, or a pharmaceutically acceptable salt thereof.

**2**. The compound according to claim **1**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of (1) a lower alkyl group, (2) a hydroxy-substituted lower alkyl group, (3) a formyl group, (4) an oxo group, (5) an amino group, (6) a hydroxy group, (7) a lower alkoxycarbonyl group, and (8) a pyrimidinyl group substituted by (i) a benzylamino group substituted by a halogen atom and a lower alkoxy group, and (ii) a cycloalkylcarbamoyl group substituted by a hydroxy group, $R^1$ is a lower alkyl group which may optionally be substituted by a group selected from the group consisting of a lower alkoxy group, a hydroxy group, a morpholinyl group, a lower alkylsulfonyl group, a di-(lower alkyl)phosphino group, a di-(lower alkyl) amino group, a pyrimidinyl-substituted lower alkylamino group, a pyridyl group, a pyridylamino group and a lower alkyl-substituted piperazinyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, an amino group, a di-(lower alkyl)amino group, a lower alkanoyl group and a cyano-substituted lower alkyl group, $R^4$ is a cycloalkyl group being substituted by a group selected from the group consisting of hydroxy group, a lower alkoxy group and a pyrimidinyloxy group, $R^2$ is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group, a halogen atom, a cyano group, a nitro group, a hydroxy group and a lower alkyl group.

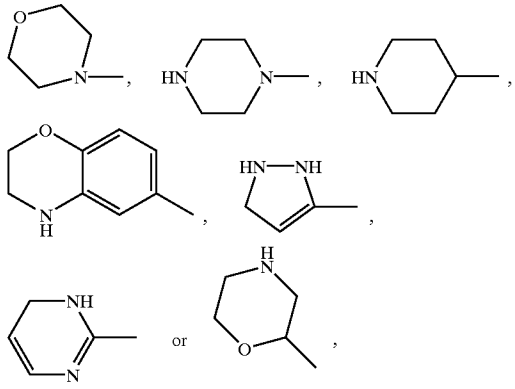
**3**. The compound according to claim **2**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group of the formula:



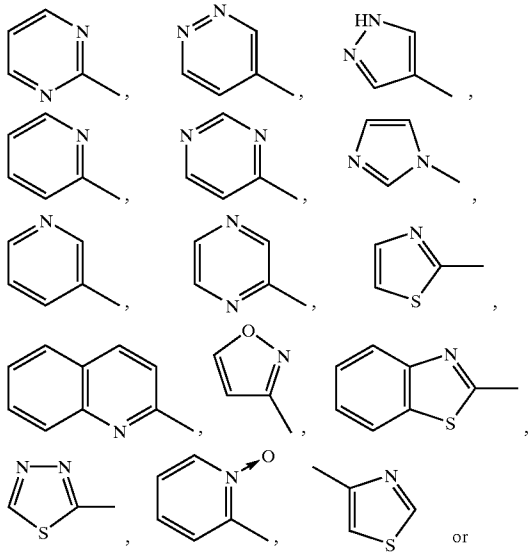
or a nitrogen-containing heterobicyclic group of the following formula wherein the above-mentioned 5- or 6-membered nitrogen-containing heteromonocyclic group and a 5- or 6-membered cyclic group are fused:



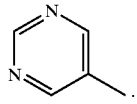
and the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a nonaromatic nitrogen-containing heteromonocyclic group of the formula:



or an aromatic nitrogen-containing heterocyclic group of the formula:



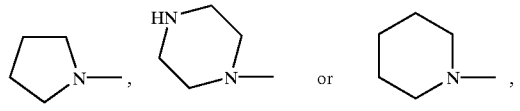
-continued



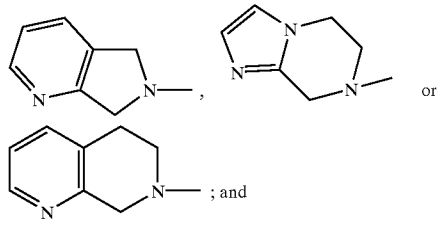
or a pharmaceutically acceptable salt thereof.

**4**. The compound according to claim **1**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, a formyl group and an oxo group, $R^1$ is a lower alkyl group which may optionally be substituted by a group selected from the group consisting of a lower alkoxy group and a morpholinyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, $R^4$ is a cycloalkyl group being substituted by a group selected from the group consisting of hydroxy group and a lower alkoxy group, $R^2$ is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group, a halogen atom and a cyano group.

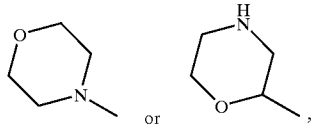
**5**. The compound according to claim **4**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



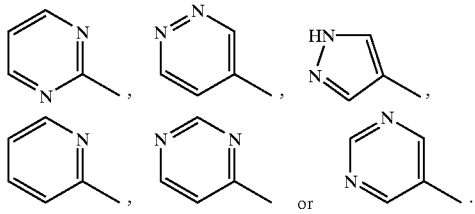
or a nitrogen-containing heterobicyclic group of the following formula wherein the above-mentioned 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group and a 5- or 6-membered aromatic nitrogen-containing heteromonocyclic group are fused:



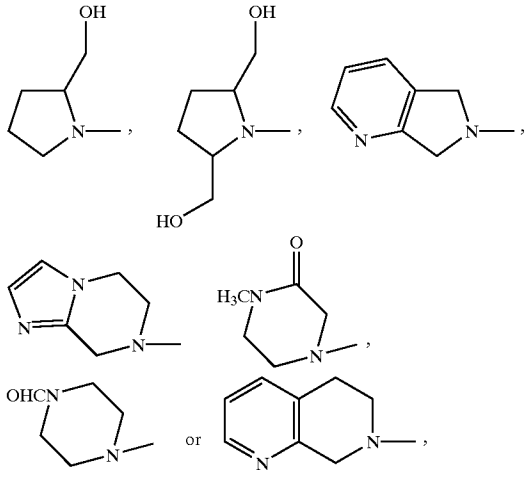
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



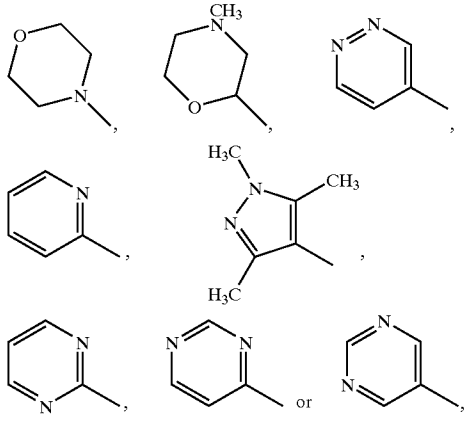
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



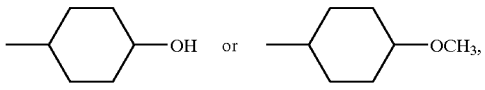
**6**. The compound according to claim **1**, wherein Ring A is a group of the formula:



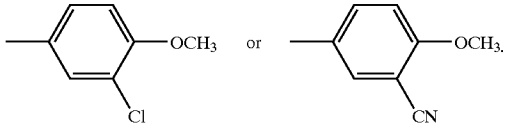
$R^1$ is a lower alkyl group, a lower alkoxy-substituted lower alkyl group, a morpholinyl-substituted lower alkyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, $R^3$ is a group of the formula:



$R^4$ is a group of the formula:

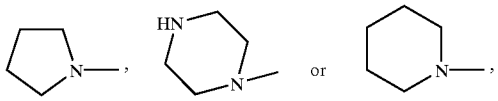


and $R^2$ is a group of the formula:

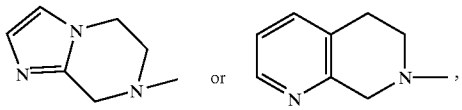


**7**. The compound according to claim **1**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is a group selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, a formyl group and an oxo group, $R^1$ is a lower alkoxy-substituted lower alkyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, $R^4$ is a hydroxy-substituted cycloalkyl group, and $R^2$ is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group and a halogen atom.

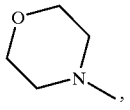
**8**. The compound according to claim **7**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



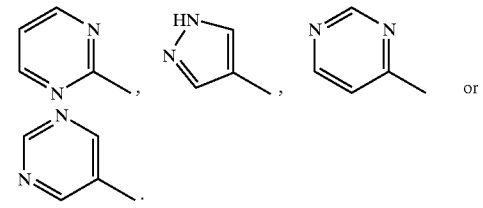
a group of the formula:



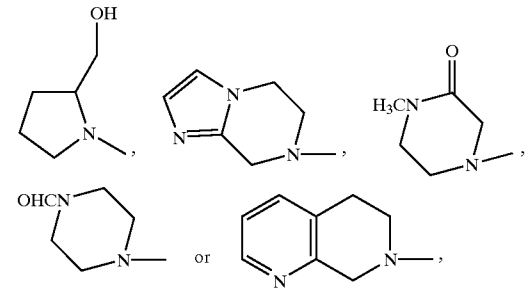
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



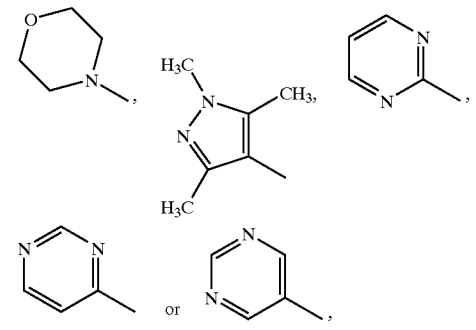
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



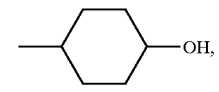
**9**. The compound according to claim **1**, wherein Ring A is a group of the formula:



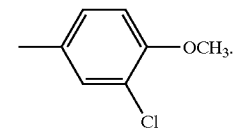
$R^1$ is a lower alkoxy-substituted lower alkyl group, a group of the formula: —NH—Q—$R^3$, or a group of the formula: —NH—$R^4$, $R^3$ is a group of the formula:



$R^4$ is a group of the formula:



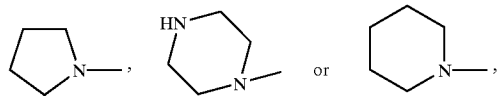
and $R^2$ is a group of the formula:



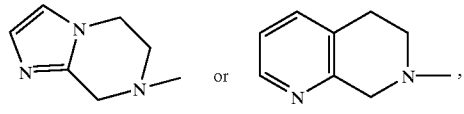
**10**. The compound according to claim **1**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is a hydroxy-substituted lower alkyl group, $R^1$ is a group of the formula: —NH—Q—$R^3$, the "substi-

tuted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, and $R^2$ is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group and a halogen atom.

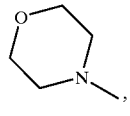
**11**. The compound according to claim **10**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



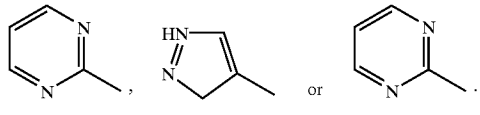
or a group of the formula:



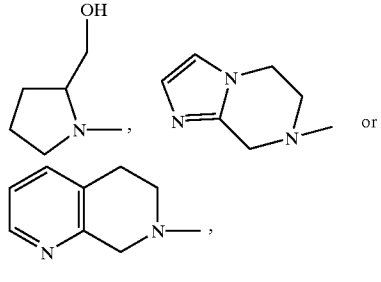
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for $R^3$ is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



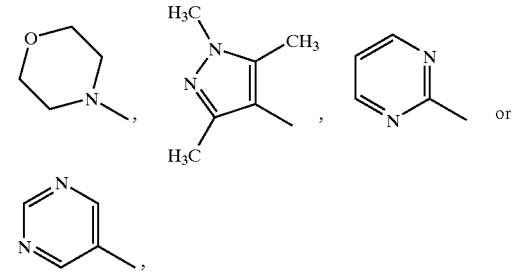
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



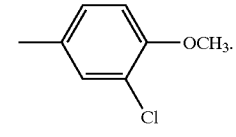
**12**. The compound according to claim **1**, wherein Ring A is a group of the formula:



$R^1$ is a group of the formula: —NH—Q—$R^3$, $R^3$ is a group of the formula:



and $R^2$ is a group of the formula:



**13**. The compound according to claim **1**, wherein said compound is selected from the group consisting of:

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidime;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-methoxycyclohexyl)carbamoyl]pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;

2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(4-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(4-methyl-3-oxo-I-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(4-formyl-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-[cis-2,5-bis(hydroxymethyl)-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine,

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-acethylpyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyridazinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridazinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[(4-methyl-2-morpholinyl)methyl]carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl] pyrimidine; and

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine,

or a pharmaceutically acceptable salt thereof.

**14**. The compound according to claim **13**, wherein said compound is selected from the group consisting of:

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)5-[N-(4-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(4-methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(4-formyl-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl] pyrimidine; and

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine,

or a pharmaceutically acceptable salt thereof.

**15**. The compound according to claim **13**, wherein said compound is selected from the group consisting of:

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5[N-(5-pyrimidinylmethyl) carbamoyl]pyrimidine; and

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine,

or a pharmaceutically acceptable salt thereof.

**16**. The compound of claim **13**, wherein said compound is (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

**17**. The compound of claim **13**, wherein said compound is 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

**18**. The compound of claim **13**, wherein said compound is (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl) carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

**19**. A pharmaceutical composition, which contains as an active ingredient the compound as set forth in any one of claims **1–12** and **13–18**, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

**20**. A method for treatment of penile erectile dysfunction, which comprises administering to a patient in need thereof an effective amount of the compound as set forth in any one of claims **1–12** and **13–18**, or a pharmaceutically acceptable salt thereof.

**21**. A method for treatment of pulmonary hypertension, which comprises administering to a patient in need thereof an effective amount of the compound as set forth in any one of claims **1–12** and **13–18**, or a pharmaceutically acceptable salt thereof.

**22**. A method for treatment of diabetic gastroparesis, which comprises administering to a patient in need thereof an effective amount of the compound as set forth in any one of claims **1–12** and **13–18**, or a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

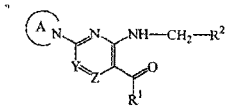
# CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.

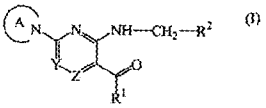


It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 76,
Lines 51-60, in the structure for formula (I):




should read

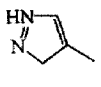



Column 79,
Line 5, after the structure

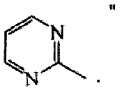

delete the period.

Column 81,
Line 47, before "a group", insert -- or --.

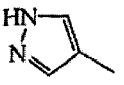
Column 83,
Lines 43-47,



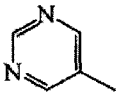

or




should read --




or




--.

Column 84,
Lines 24-26, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidime;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
Lines 40-42, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)4-(chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine; --.
Lines 43-45, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 46-48, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 49-51, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(pyrimidinylmethyl)carbamoyl]pyrimidine; --

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 84 (cont'd),
Lines 52-54, "2-(4methyl-3-oxo-I-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;" should read -- 2-(4methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl) carbamoyl]pyrimidine; --
Line 64, replace the comma "," with a semicolon -- ; --.
Lines 65-67, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

Column 85,
Lines 1-3, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 13-15, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridazinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine; --
Lines 16-18, "(S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbomoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl)carbomoyl] pyrimidine; --.
Lines 19-21, "(S)-2-(2-hydroxymethyl-1-pyrrolidiny)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidiny)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl)carbonoy]pyrimidine; --.
Lines 22-24, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine; --
Lines 38-40, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino) 5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
Lines 48-50, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.



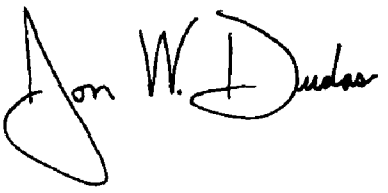
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 85 (cont'd),
Lines 51-53, "2-(5,6,7,8-tetrahydroimidazo[1-2-a]pyrazine-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyridine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1-2-a]pyrazine-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyridine; --.
Lines 54-56, "2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 57-59, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-pyridinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridinylmethyl)carbamoyl]pyrimidine; --.

Column 86,
Lines 1-3, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, --.
Lines 19-21, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

Signed and Sealed this

Twenty-eighth Day of September, 2004



JON W. DUDAS
*Director of the United States Patent and Trademark Office*

UNITED STATES PATENT AND TRADEMARK OFFICE

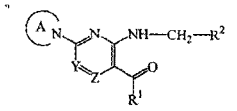
# CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.

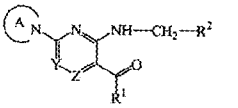


It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 76,
Lines 51-60, in the structure for formula (I):



(I) should read



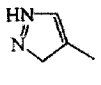
(I)

Column 79,
Line 5, after the structure

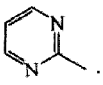
delete the period.

Column 81,
Line 47, before "a group", insert -- or --.

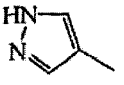
Column 83,
Lines 43-47,



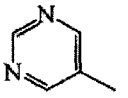
or



should read --



or



--.

Column 84,
Lines 24-26, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidime;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
Lines 40-42, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)4-(chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl) (3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 43-45, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 46-48, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 49-51, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(pyrimidinylmethyl)carbamoyl]pyrimidine; --

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 84 (cont'd),
Lines 52-54, "2-(4methyl-3-oxo-I-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;" should read -- 2-(4methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl) carbamoyl]pyrimidine; --
Line 64, replace the comma "," with a semicolon -- ; --.
Lines 65-67, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

Column 85,
Lines 1-3, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 13-15, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridazinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine; --
Lines 16-18, "(S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbomoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl)carbomoyl] pyrimidine; --.
Lines 19-21, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl)carbonyl]pyrimidine; --.
Lines 22-24, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine; --
Lines 38-40, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino) 5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
Lines 48-50, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

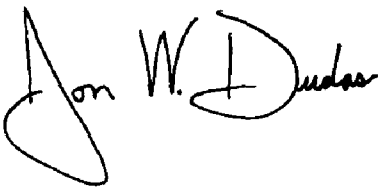
Column 85 (cont'd),
Lines 51-53, "2-(5,6,7,8-tetrahydroimidazo[1-2-a]pyrazine-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyridine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1-2-a]pyrazine-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyridine; --.
Lines 54-56, "2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 57-59, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-pyridinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridinylmethyl)carbamoyl]pyrimidine; --.

Column 86,
Lines 1-3, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, --.
Lines 19-21, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

This certificate supersedes Certificate of Correction issued September 28, 2004.

Signed and Sealed this

Thirtieth Day of November, 2004



JON W. DUDAS
*Director of the United States Patent and Trademark Office*

UNITED STATES PATENT AND TRADEMARK OFFICE

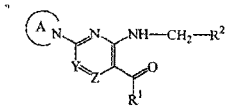
# CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.

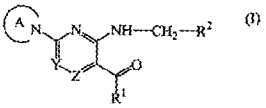


It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 76,
Lines 51-60, in the structure for formula (I):




should read

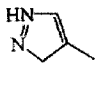



Column 79,
Line 5, after the structure

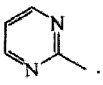

delete the period.

Column 81,
Line 47, before "a group", insert -- or --.

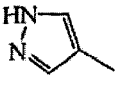
Column 83,
Lines 43-47,



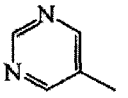

or




should read --




or




--.

Column 84,
Lines 24-26, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidime;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
Lines 40-42, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)4-(chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 43-45, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 46-48, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 49-51, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(pyrimidinylmethyl)carbamoyl]pyrimidine; --

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 84 (cont'd),
Lines 52-54, "2-(4methyl-3-oxo-I-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;" should read -- 2-(4methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl) carbamoyl]pyrimidine; --
Line 64, replace the comma "," with a semicolon -- ; --.
Lines 65-67, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

Column 85,
Lines 1-3, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 13-15, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridazinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine; --
Lines 16-18, "(S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbomoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl)carbomoyl] pyrimidine; --.
Lines 19-21, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl)carbonyl]pyrimidine; --.
Lines 22-24, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine; --
Lines 38-40, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino) 5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
Lines 48-50, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

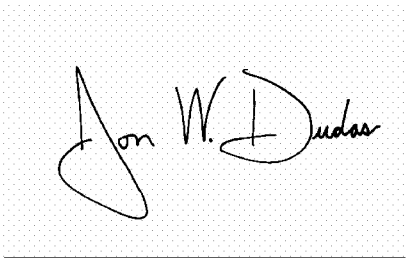
Column 85 (cont'd),
Lines 51-53, "2-(5,6,7,8-tetrahydroimidazo[1-2-a]pyrazine-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyridine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1-2-a]pyrazine-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyridine; --.
Lines 54-56, "2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 57-59, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-pyridinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridinylmethyl)carbamoyl]pyrimidine; --.

Column 86,
Lines 1-3, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, --.
Lines 19-21, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

This certificate supersedes Certificate of Correction issued September 28, 2004 and November 30, 2004.

Signed and Sealed this

Third Day of May, 2005



JON W. DUDAS
*Director of the United States Patent and Trademark Office*

# UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

| | | | |
|---|---|---|---|
| (68) | PATENT NO. | : | 6,656,935 |
| (45) | ISSUED | : | December 2, 2003 |
| (75) | INVENTOR | : | Koichiro Yamada et al. |
| (73) | PATENT OWNER | : | Mitsubishi Tanabe Pharma Corp. |
| (95) | PRODUCT | : | STENDRA® (avanafil) |

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 6,656,935 based upon the regulatory review of the product STENDRA® (avanafil) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,687 days

from September 13, 2020, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 16th day of March 2016.

Michelle K. Lee

Michelle K. Lee
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

EXHIBIT B

Orange Book listing for STENDRA® avanafil

# Patent and Exclusivity for: N202276

Product 001
AVANAFIL (STENDRA) TABLET 50MG

## Patent Data

| Product No | Patent No | Patent Expiration | Drug Substance | Drug Product | Patent Use Code | Delist Requested |
|---|---|---|---|---|---|---|
| 001 | 6656935 | 04/27/2025 | DS | DP | U-155 | |
| 001 | 7501409 | 05/05/2023 | | DP | | |

## Exclusivity Data

| Product No | Exclusivity Code | Exclusivity Expiration |
|---|---|---|

There is no unexpired exclusivity for this product in the Orange Book database.

View a list of all patent use codes (results_patent.cfm)
View a list of all exclusivity codes (results_exclusivity.cfm)

EXHIBIT C

Empower website page

EmpoweRx PHARMACY

FDA 503B REGISTERED

PCAB ACCREDITED Compounding Pharmacy

Drug Catalog

Where We Ship

PRODUCTS

COMPANY

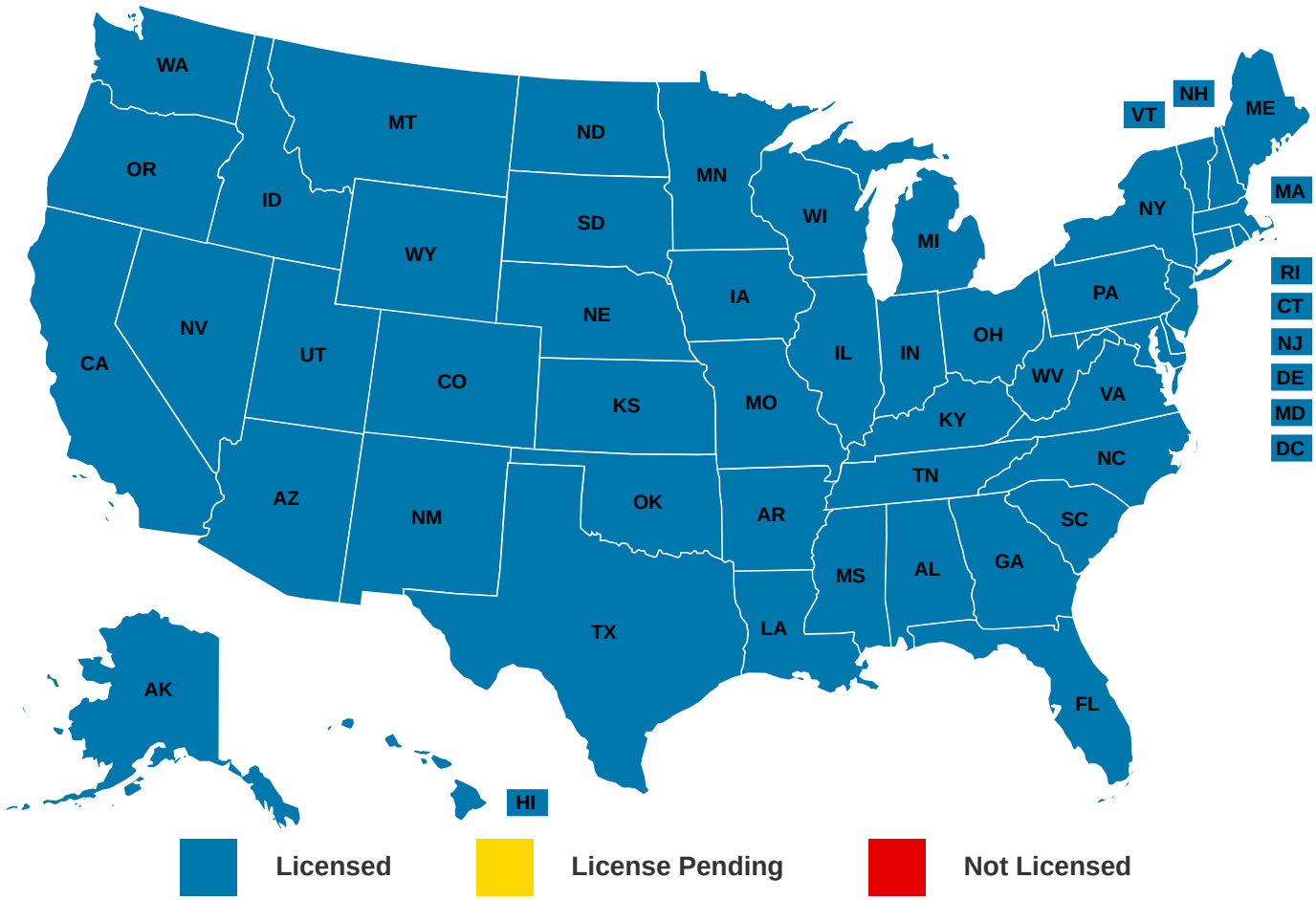
QUALITY

CONTACT US

PRESCRIPTION REFILL

PRESCRIBER LOGIN

# Licensed States




## We are licensed to ship to all 50 states:

**Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin and Wyoming**

**Whenever, Wherever.** Using a national in-house computer tracking system, Empower Pharmacy delivers Ground or Overnight, six days a week. You can be confident the medications will be delivered when needed.

**We Respect Your Privacy.** Empower Pharmacy packages deliveries in discreet boxes so your personal business remains private.

**Dedicated and Professional.** Empower Pharmacy's team of certified compounding pharmacists are ready to answer questions, provide training and deliver highly specialized compounding services. They are ready to help guide patients through the administration of their dosage forms and provide the necessary usage instructions as well as support.

**Free Supplies.** We provide all the necessary supplies such as syringes, alcohol wipes, needles and reconstitution kits (prescription required). We also give our patients complimentary instruction pamphlets and documents. This translates to significant money savings and peace of mind that patients are administering their medications properly.

EXHIBIT D

Empower catalog page

# Urology Product Catalog

**EmpoweR PHARMACY**

empowerpharmacy.com

5980 W Sam Houston Pkwy N, Suite 300
Houston, TX 77041

832.678.4417 Phone
832.678.4419 Fax
877.562.8577 Toll Free

Hours: M-F 8:30am - 5:30pm CT
Sat 8:30am - 1:30pm CT

## Capsules & Tablets

| PRODUCT NAME | STRENGTH | SIZE | PRICE |
|---|---|---|---|
| Anastrozole | 0.125 mg | Each | $0.70 |
| | 0.25 mg | Each | $0.75 |
| | 0.5 mg | Each | $0.80 |
| | 0.75 mg | Each | $1.00 |
| | 1 mg | Each | $1.50 |
| Armour Thyroid | 0.5 Grain | Each | Market |
| | 1 Grain | Each | Market |
| | 1.5 Grain | Each | Market |
| | 2 Grain | Each | Market |
| | 3 Grain | Each | Market |
| Biotin / Finasteride | 5/1 mg | Each | $1.50 |
| Cabergoline | 0.5 mg | Each | Market |
| Cialis | 5 mg | Each | Market |
| | 20 mg | Each | Market |
| Clomiphene Citrate | 12.5 mg | Each | $1.50 |
| | 25 mg | Each | $1.70 |
| | 50 mg | Each | $2.00 |
| Danazol | 25 mg | Each | $1.75 |
| | 75 mg | Each | $2.00 |
| Desiccated Thyroid | 15 mg | Each | $0.50 |
| | 30 mg | Each | $0.50 |
| | 45 mg | Each | $0.55 |
| | 60 mg | Each | $0.65 |
| | 90 mg | Each | $0.85 |
| | 120 mg | Each | $1.05 |
| DHEA (IR / SR) | 5 mg | Each | $0.50 |
| | 10 mg | Each | $0.50 |
| | 25 mg | Each | $0.65 |
| | 50 mg | Each | $0.75 |
| | 100 mg | Each | $0.90 |
| Finasteride | 1 mg | Each | Market |
| | 5 mg | Each | Market |
| Ibutamoren Mesylate | 12.5 mg | Each | $3.04 |
| | 25 mg | Each | $4.83 |
| Letrozole | 2.5 mg | Each | $1.00 |
| Levitra | 20 mg | Each | Market |
| Oxandrolone | 5 mg | Each | $1.00 |
| | 15 mg | Each | $1.00 |
| | 25 mg | Each | $1.00 |
| | 50 mg | Each | $1.00 |

## Capsules & Tablets

| PRODUCT NAME | STRENGTH | SIZE | PRICE |
|---|---|---|---|
| Sildenafil SR | 36 mg | Each | $2.00 |
| | 75 mg | Each | $3.00 |
| | 110 mg | Each | $4.50 |
| Sildenafil / Tadalafil | 55/12.5 mg | Each | $3.83 |
| Tadalafil SR | 3 mg | Each | $1.35 |
| | 7 mg | Each | $2.35 |
| | 12 mg | Each | $3.50 |
| | 25 mg | Each | $5.00 |
| Tamoxifen Citrate | 10 mg | Each | $1.00 |
| | 20 mg | Each | $1.50 |
| Viagra | 100 mg | Each | Market |
| Yohimbine HCl | 5.4 mg | Each | $1.25 |

## Orally Disintegrating Tablets

| PRODUCT NAME | STRENGTH | SIZE | PRICE |
|---|---|---|---|
| Avanafil | 250 mg | Each | $5.50 |
| Sildenafil | 125 mg | Each | $5.50 |
| Tadalafil | 25 mg | Each | $5.50 |
| Vardenafil | 25 mg | Each | $5.50 |

## Troches

| PRODUCT NAME | STRENGTH | SIZE | PRICE |
|---|---|---|---|
| Avanafil | 200 mg | Each | $6.10 |
| Oxytocin | 50 IU | Each | $2.70 |
| Sildenafil | 50 mg | Each | $4.30 |
| | 100 mg | Each | $6.10 |
| Sildenafil / Testosterone Troche (Low Dose-Women) | 20/20 mg | Each | $8.00 |
| Sildenafil / Testosterone Troche (Men) | 100/100 mg | Each | $12.00 |
| Tadalafil | 10 mg | Each | $4.30 |
| | 20 mg | Each | $6.10 |
| Vardenafil | 10 mg | Each | $4.30 |
| | 20 mg | Each | $6.10 |

EXHIBIT E

Plaintiff's cease and desist request

**PHARMACEUTICAL PATENT ATTORNEYS, LLC**
*www.LicensingLaw.Net*

55 Madison Avenue, 4th floor
Morristown, NJ 07960-7397 USA

Practice limited to Domestic & International Pharmaceutical Patent law

01 June 2018

Mr. Shaun NOORIAN, Owner
Empower Rx Pharmaceuticals LLC
5980 Sam Houston Parkway N, Suite 300
Houston, TX 77041 USA
BY PRIORITY MAIL

Re: Avanafil 200 mg oral disintegrating tablets and troches
United States Letters Patent No. 6656935

Dear Shaun,

Congratulations on building a successful business. I write to ask your help to resolve an issue. Your *Urology Product Catalog* (copy attached) offers for sale avanafil. Avanafil, however, is patented. *See* United States Letters Patent No. 6656935 (copy attached). Selling avanafil infringes this patent.

Pharmaceutical patent litigation can easily cost you over five million dollars in legal fees. To avoid this expense, within seven (7) calendar days of receipt of this letter:

1. Confirm in writing that you no longer offer avanafil for sale.
2. Confirm in writing that you have removed avanafil products from your catalog, and provide a copy of your corrected catalog showing this.
3. Provide complete formulations for each of the captioned finished dosage forms.
4. Turn over all of your remaining inventory of avanafil (both as API and compounded into finished dosage form).
5. Provide records of each of your purchases of avanafil API, showing the dates, quantities and source of this API.
6. Provide an accounting of all of your sales of avanafil, showing the dates, quantities, prices, dosage forms and location (city and state) of the purchaser.

As an aside, before launching new products in the future, it might be useful for you to first review the FDA's *Orange Book* to see whether the product might be patented. The *Orange Book*, for example, lists the captioned patent. Reviewing the *Orange Book* before selling avanafil could have spared you this potentially-expensive legal headache.

If you have any questions, please let me know. I look forward to hearing from you within seven days.

Sincerely,

PHARMACEUTICAL PATENT ATTORNEYS, LLC

Mark Pohl, Esq.
☎ +1 (973) 984-6159 x304
Mark.Pohl@LicensingLaw.Net

Enclosures
United States Letters Patent No. 6656935

Cc: Greg FORD
Regina MIRRA
Ms. Vi LI, Managing Member, Empower Rx Pharmacy LLC, 20018 Cypresswood Lake Drive, Spring, TX 77373 USA

UNITED STATES POSTAL SERVICE

Date: June 4, 2018

Mark POHL:

The following is in response to your June 2, 2018 request for delivery information on your Signature Confirmation™/Insured <= $500 item number 940780369930004007697l. The delivery record shows that this item was delivered on June 4, 2018 at 12:39 pm in HOUSTON, TX 77041 to S NOORIAN. There is no delivery signature on file for this item.

Thank you for selecting the Postal Service for your mailing needs. If you require additional assistance, please contact your local Post Office or postal representative.

Sincerely,
United States Postal Service

EXHIBIT F

Orange Book listing for QSYMIA®

# Patent and Exclusivity for: N022580

Product 001
PHENTERMINE HYDROCHLORIDE; TOPIRAMATE (QSYMIA)
CAPSULE, EXTENDED RELEASE EQ 3.75MG BASE;23MG

## Patent Data

| Product No | Patent No | Patent Expiration | Drug Substance | Drug Product | Patent Use Code | Delist Requested |
|---|---|---|---|---|---|---|
| 001 | 7056890 | 06/14/2020 | | DP | U-1262 | |
| 001 | 7553818 | 06/14/2020 | | | U-1262 | |
| 001 | 7659256 | 06/14/2020 | | DP | U-1262 | |
| 001 | 7674776 | 06/14/2020 | | DP | U-1262 | |
| 001 | 8580298 | 05/15/2029 | | DP | | |
| 001 | 8580299 | 06/14/2029 | | | U-1262 | |
| 001 | 8895057 | 06/09/2028 | | | U-1262 | |
| 001 | 8895058 | 06/09/2028 | | DP | | |
| 001 | 9011905 | 06/09/2028 | | DP | | |
| 001 | 9011906 | 06/09/2028 | | | U-1262 | |

## Exclusivity Data

| Product No | Exclusivity Code | Exclusivity Expiration |
|---|---|---|

There is no unexpired exclusivity for this product in the Orange Book database.

View a list of all patent use codes (results_patent.cfm)
View a list of all exclusivity codes (results_exclusivity.cfm)

EXHIBIT G

Vivus Therapeutics' cease and desist request

**VIVUS, Inc.**
900 E. Hamilton Ave., Suite 550, Campbell, California 95008 | TEL (650) 934-5200

WRITER'S DIRECT DIAL NO.
**(650) 934-5306**

WRITER'S EMAIL ADDRESS
**wells@vivus.com**

March 30, 2018

**VIA UPS**

Shaun Noorian, CEO
Empower Clinical Services, LLC
dba Empower Pharmacy
5980 W Sam Houston Pkwy N
Suite 300
Houston, TX 77041

Re: U.S. Patents Covering Pharmaceutical Compositions Comprising Phentermine HCl and Topiramate

Dear Mr. Noorian:

I represent VIVUS, Inc. ("VIVUS") as intellectual property counsel. It has come to our attention that you are compounding and offering for sale, through EmpowerRX, a pharmaceutical composition comprised of phentermine HCl and topiramate for weight management. Based on your "Patient Product Catalog" (02.19) as well as your "Clinic Product Catalog" (02.19.3) on pages 5 and 3, respectively, you are offering for sale products you refer to as "Phentermine HCl/Topiramate" at the following strengths 15/12.5, 15/25, 30/25, 30/50, 45/25 and 45/50 mg.

VIVUS is the owner of U.S. Patent Nos 7,553,818 ("the '818 patent"), 7,659,256 ("the '256 patent") and 7,674,776 ("the '776 patent") covering, among other things, pharmaceutical compositions comprised of phentermine in combination with topiramate. Copies of the '818 patent, the '256 patent and the '776 patent are enclosed for your reference.

We believe that by your activity, you have infringed, and continue to infringe, the '818 patent, the '256 patent and the '776 patent pursuant to 35 U.S.C. § 271. Accordingly, you should immediately cease and desist from offering your "Phentermine HCl/Topiramate" combinations for sale and provide to me via email a copy of your revised patient and clinic product catalogs once these products have been removed.

I would also like to take this opportunity to make sure that you are aware that QSYMIA® (phentermine and topiramate extended-release) is subject to a risk evaluation and mitigation strategy (REMS) with the goal of informing prescribers and female patients of reproductive

Sean Noorian
March 30, 2018

potential about (i) the increased risk of congenital malformation in infants exposed to QSYMIA during the first trimester of pregnancy, (ii) the importance of pregnancy prevention for females of reproductive potential receiving QSYMIA and (iii) the need to discontinue QSYMIA immediately if pregnancy occurs. The REMS program has been put in place to mitigate the risk of birth defects and includes elements to assure safe use that limit dispensing of QSYMIA to only certified pharmacies that agree to distribute the QSYMIA Medication Guide and the *Risk of Birth Defects with Qsymia* patient brochure each time QSYMIA is dispensed and to maintain a list of QSYMIA prescribers. The FDA made the determination that a REMS was required for safe distribution of QSYMIA and in the event a generic equivalent to QSYMIA is approved in the future the generic manufacturer would also be required to provide a comparable REMS program.

The QSYMIA REMS program, like many REMS, is a complex program that is specifically designed to ensure patient safety with respect to a drug that poses a heightened safety risk. VIVUS has worked diligently to establish an appropriate risk management plan to address these heightened risks and to allow patients to safely receive the benefits of QSYMIA and mitigate VIVUS's liability risks. Your distribution of "Phentermine HCl/Topiramate" subverts the QSYMIA REMS program and potentially exposes patients to safety risks.

We hope that this matter can be resolved amicably without resorting to any of the legal and equitable remedies that are available to VIVUS to protect our intellectual property rights relating to pharmaceutical compositions comprised of phentermine in combination with topiramate. Please contact me immediately so that we can discuss the resolution of this matter.

Very truly yours,

Sandra Wells

Sandra Wells
VP Patents & Assistant General Counsel

Enclosures:

U.S. Patent Nos. 7,553,818, 7,659,256 and 7,674,776

EXHIBIT H

Proposed Order

J. Mark Pohl
Pharmaceutical Patent Attorneys, LLC
55 Madison Avenue, 4th floor
Morristown, NJ 07960
(973) 984-6159 x304
Attorneys for Plaintiff

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

| | |
|---|---|
| METUHEN PHARMACEUTICALS, LLC<br><br>Plaintiff,<br><br>vs.<br><br>EMPOWER PHARMACEUTICALS LLC<br>EMPOWER CLINICAL SERVICES LLC<br>SHAUN NOORIAN and<br>ARTA S. NOORIAN<br><br>Defendants | Civil Action No. _____<br>Hon. _____ |

**ORDER**

THIS MATTER having been opened to the Court by plaintiff Metuchen Pharmaceuticals LLC,

and the Court having heard arguments submitted by and considered evidence submitted by Plaintiff and, if any, by Empower Pharmaceuticals LLC, Empower Clinical Services LLC, Shaun Noorian and Arta S. Noorian (collectively, the "Defendants")

and the Court having found good cause,

IT IS ORDERED:

A) Defendants are hereby enjoined from importing, making, offering for sale or selling any product containing avanafil until the expiration of United States letters patent no. 6656935.

B) Defendants must within 14 calendar days provide to Plaintiff the complete formulation for each finished dosage form each of the Defendants' avanafil products.

C) Defendants must within 14 calendar days turn over to Plaintiff all of Defendants' inventory of avanafil (both as Active Pharmaceutical Ingredient ("API") and compounded into finished dosage form).

D) Defendants must within 14 calendar days provide to Plaintiff a list of each of Defendants' purchases of avanafil API, and provide to Plaintiff photocopies of all documentation accompanying each API delivery, showing the date the API was delivered to Defendant, the quantity of API delivered, the API vendor, the API manufacturer and the *Certificate of Analysis* for each delivery.

E) Defendants must within 14 calendar days provide to Plaintiff an accounting of all of Defendants' sales of avanafil, showing the dates, quantities, prices, dosage forms and location (city and state) of the purchaser.

F) Defendants' infringement is "exceptional" within the meaning of 35 U.S.C. § 285. Defendants must thus within 14 calendar days reimburse Plaintiff its reasonable attorneys fees.

G) To encourage compliance with this Order, the Court here grants Plaintiff a first priority security interest in all of Defendants' property, both real and personal.

ORDERED that a copy of this Order shall be circulated within seven calendar days hereof.

_____

Hon. _____, U.S.D.J.