EUROPEAN PATENT SPECIFICATION

AROMATIC NITROGENOUS SIX-MEMBERED RING COMPOUNDS
AROMATISCHE STICKSTOFFHÄLTIGE SECHS-RING-VERBINDUNGEN
COMPOSES CYCLIQUES AROMATIQUES AZOTES A SIX ELEMENTS

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Description

TECHNICAL FIELD

[0001] 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

[0002] 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.

[0003] 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 and pulmonary hypertension (cf., PCT Patent Publication WO 96/05176), 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)).

[0004] 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), (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)).

[0005] However, sildenafil has been reported to have side effects such as headache, facial suffusion, gut disorder, rhinitis, color sense disorder, and penile erectile continuance (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)).

[0006] 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 (Morales 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)).

[0007] The present invention relates to an aromatic nitrogen-containing 6-membered cyclic compound of the formula (I):

\[
\begin{align*}
A & \quad \text{Ring A is a 5- to 10-membered mono- or bicyclic nitrogen-containing heterocycle optionally substituted with C}_{1-6}\text{-alkyl optionally substituted with hydroxy or cyano, formyl, oxo, amino, di(C}_{1-6}\text{-alkyl)}\text{amino, hydroxy, C}_{1-6}\text{-alkoxy, C}_{1-6}\text{-alkoxycarbonyl, optionally (C}_{1-6}\text{-alkoxy)}\text{-substituted C}_{1-6}\text{-alkanoyl, or pyrimidinyl substituted with (i) benzylamino substituted with a halogen atom and C}_{1-6}\text{-alkoxy and (ii) hydroxy- substituted cycloalkylcarbamoyl,}
\end{align*}
\]

\[
R^1 \quad \text{is selected from}
\]

\[
\text{NHLCH}_2-\text{R}^2
\]
C_{1-6}-alkyl optionally substituted with C_{1-6}-alkoxy, hydroxy, morpholinyl, C_{1-6}-alkylsulfonyl, di(C_{1-6}-alkyl)phosphino, di(C_{1-6}-alkyl)amino, pyrimidinyl-(C_{1-6}-alkyl)amino, pyridyl, pyridylamino, (C_{1-6}-alkyl)piperazinyl or pyrimidinyloxy;

-NH-Q-R^3, wherein Q is C_{1-6}-alkylene or a single bond, and R^3 is a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic nitrogen-containing heterocycle optionally substituted with C_{1-6}-alkyl optionally substituted with hydroxy or cyano, formyl, oxo, amino, di(C_{1-6}-alkyl)amino, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkoxycarbonyl, optionally (C_{1-6}-alkoxy)-substituted C_{1-6}-alkanoyl, or pyrimidinyl substituted with (i) benzylamino substituted with a halogen atom and C_{1-6}-alkoxy and (ii) hydroxy-substituted cycloalkylcarbamoyl; and

-NH-R^4, wherein R^4 is C_{3-8}-cycloalkyl optionally substituted with C_{1-6}-alkoxy, hydroxy, morpholinyl, C_{1-6}-alkylsulfonyl, di(C_{1-6}-alkyl)phosphino, di(C_{1-6}-alkyl)amino, pyrimidinyl-(C_{1-6}-alkyl)amino, pyridyl, pyridylamino, (C_{1-6}-alkyl)piperazinyl or pyrimidinyloxy;

R^2 is 5- to 10-membered mono- or bicyclic aryl optionally substituted with C_{1-6}-alkoxy, halogen, cyano, nitro, hydroxy or C_{1-6}-alkyl; and

one of Y and Z is =CH- and the other is =N-; or a pharmaceutically acceptable salt thereof.

[0008] In the compounds (I) of the present invention, 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, piperazinyl, piperidyl or morpholinyl, a 5- or 6-membered aromatic nitrogen-containing heteromono-cyclic group such as imidazolyl or pyrrolyl, and a nitrogen-containing heterobicyclic group such as 6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl, 5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl, 1,2,3,4-tetrahydro-2-isquinolinol, 1H-2,3,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-yl, 4,5,6,7-tetrahydropropyridin[4,3-d]pyrimidine-6-yl, or 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-3-yl.

[0009] R^2 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 heteromonocyclic group such as morpholinyl, piperazinyl, piperidyl, thiazolidinyl, dihydropyrimidinyl or dihydropyrazolyl, a 5- or 6-membered aromatic nitrogen-containing heteromonocyclic group such as pyrimidinyl, pyridazinyl, pyridyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl or pyrazinyl, and a 8- to 10-membered nitrogen-containing heterobicyclic group such as benzothiazolyl, quinolyl or dihydrobenzoxazolyl.

[0010] The optional substituent of Ring A and R^3 is as defined above.

[0011] R^2 is a 5- to 10-membered monocyclic or bicyclic aromatic hydrocarbon group such as phenyl or naphthyl.

[0012] The optional substituent of R^2 is as defined above.

[0013] The optional substituent of R^1 and the optional substituent of R^4 are as defined above.

[0014] Throughout the present description and the claims, the C_{1-6}-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 or tert-butyl. The C_{1-6}-alkoxy group* means a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, such as methoxy, ethoxy, propanoyle, isopropyleoxy, butyloxy, isobutyloxy or tert-butoxy.

[0015] The C_{3-8}-cycloalkyl group* means a cycloalkyl having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. The C_{3-8}-cycloalkylene group* means a straight chain or branched chain cycloalkylene group having 1 to 6 carbon atoms, such as methylene, ethylene or trimethylene.

[0016] The "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom.

[0017] Among the compounds (I) of the present invention, preferable, more preferable and especially preferred are the following : compounds of the formula (I):

(1) The compounds of formula (I), wherein ring A is a nitrogen-containing 5- or 6-membered heteromonocycle or a 8- to 10-membered heterobicycle, each optionally substituted with C_{1-6}-alkyl optionally substituted with hydroxy, formyl, oxo, amino, hydroxy, C_{1-6}-alkoxycarbonyl, or pyrimidinyl substituted with (i) benzylamino substituted with a halogen atom and C_{1-6}-alkoxy and (ii) hydroxy-substituted cycloalkylcarbamoyl, R^1 is selected from C_{1-6}-alkyl optionally substituted with C_{1-6}-alkoxy, hydroxy, morpholinyl, C_{1-6}-alkylsulfonyl, di(C_{1-6}-alkyl)phosphino, di(C_{1-6}-alkyl)amino, pyrimidinyl-(C_{1-6}-alkyl)amino, pyridyl, pyridylamino, (C_{1-6}-alkyl)piperazinyl or pyrimidinyloxy; and

R^2 is phenyl substituted with C_{1-6}-alkoxy, halogen, cyano, nitro, hydroxy or C_{1-6}-alkyl.
(2) The compounds as in item (1), wherein ring A is an optionally substituted heterocycle selected from and R³ is an optionally substituted heterocycle selected from
(3) The compounds as in item (1), wherein the optional substituent of ring A is selected from C_{1-6}-alkyl optionally substituted with hydroxy, formyl, and oxo;
R^1 is selected from C_{1-6}-alkyl optionally substituted with C_{1-6}-alkoxy or morpholinyl; -NH-Q-R^3, wherein R^3 is a nitrogen-containing 5- or 6-membered heteromonocycle optionally substituted with C_{1-6}-alkyl; and -NH-R^4, wherein R^4 is cycloalkyl optionally substituted with C_{1-6}-alkoxy or hydroxy; and
R^2 is phenyl substituted with C_{1-6}-alkoxy, halogen or cyano.

(4) The compounds as in item (3), wherein ring A is an optionally substituted heterocycle selected from

![Chemical Structures](image)

and R^3 is an optionally substituted heterocycle selected from

![Chemical Structures](image)

(5) The compounds of formula (I), wherein ring A is selected from

![Chemical Structures](image)

R^1 is C_{1-6}-alkyl, (C_{1-6}-alkoxy)C_{1-6}-alkyl, morpholinyl-C_{1-6}-alkyl, a group -NH-Q-R^3, wherein R^3 is selected from
or \(-\text{NH-R}_4\), wherein \(R_4\) is

and \(R_2\) is

(6) The compounds as in item (3), wherein \(R_1\) is selected from \((\text{C}_1-\text{C}_6\text{-alkoxy})\text{C}_1-\text{C}_6\text{-alkyl}\), \(-\text{NH-Q-R}_3\), wherein \(R_3\) is a nitrogen-containing 5- or 6-membered heteromonocycle optionally substituted with \(\text{C}_1-\text{C}_6\text{-alkyl}\), and \(-\text{NH-R}_4\), wherein \(R_4\) is hydroxy-substituted cycloalkyl; and \(R_2\) is phenyl substituted with \(\text{C}_1-\text{C}_6\text{-alkoxy}\) or halogen.

(7) The compounds as in item (6), wherein ring A is an optionally substituted heterocycle selected from:

and

and \(R_3\) is an optionally substituted heterocycle selected from:
(8) The compounds as in item (5), wherein ring A is selected from:

(9) The compounds as in item (3), wherein the optional substituent of Ring A is hydroxy-substituted C_{1-6}-alkyl; R^1 is -NH-Q-R^3; and R^2 is phenyl substituted with C_{1-6}-alkoxy or halogen.

(10) The compounds as in item (9), wherein Ring A is an optionally substituted heterocycle selected from
(11) The compounds as in item (8), wherein Ring A is selected from:

and

R₁ is -NH-Q-R³ wherein R³ is selected from

and

R² is 3-chloro-4-methoxyphenyl.

(12) The compounds as in any one of items (1)-(11), wherein Y = N- and Z = CH-.

(13) The following compounds of formula (I) or pharmaceutically acceptable salts 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-4methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

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

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

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4methoxybenzylamino)-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-[3R]-4-methyl-2-morpholinoethyl]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-(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-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-tetrahydroimidazo[1,2-a]pyrazin-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-acetylpyrimidine;

(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-(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-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine; and

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine.
The following compounds of formula (I) or pharmaceutically acceptable salts 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-pyridinylmethyl)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-(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.

The following compounds of formula (I) or pharmaceutically acceptable salts 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; and
When the compound (I) of the present invention or a pharmaceutically acceptable salt thereof (in the following term "compound (I) will be used for the same of brevity. It includes the present compounds (I) and pharmaceutically acceptable salts, where applicable) has an asymmetric carbon atom at Ring A, R1 and/or R2, 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) 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) 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, jellies, suppositories, ointments, elixirs, liniments, lotions, drinks, nasal drops, percutaneous preparations, and rapidly-disintegrating tablets in oral cavity. These pharmaceutical preparations may be prepared by formulating with a pharmaceutically acceptable additive such as excipient, binder, wetting agent, disintegrator or thickening agent, by a conventional method.

The dose of the compound (I) 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) 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) may be prepared by the following Processes A to F. Therein, the substituents R1-R4, Y, Z and ring A one as defined in formula (I) if not indicated otherwise. Also, in the reaction schemes identical symbols have identical meanings if not indicated otherwise.

Process A

Among the compounds (I) of the formula (I) wherein R1 is -NH-Q-R3 or -NH-R4, i.e., the compound of the formula (I-a):
(wherein R^{11} is -NH-Q-R^3 or -NH-R^5) can be prepared by reacting a compound of the formula (II):

\[
\begin{align*}
\text{(II)} & \\
\text{wherein } X^1 \text{ is a halogen atom, } R^5 \text{ is a protecting group for carboxyl group, } R^9 \text{ is substituted or unsubstituted } C_{1-6}\text{-alkyl group or a substituted or unsubstituted aryl group,} \\
& \text{with a compound of the formula (III):} \\
R^2\text{-CH}_2\text{-NH}_2 & \quad \text{(III)}
\end{align*}
\]

oxidizing the resulting compound of the formula (IV):

\[
\begin{align*}
\text{(IV)} & \\
& \text{to give a sulfonyl (or sulfnyl) compound of the formula (V):} \\
& \text{wherein } n \text{ is 1 or 2,} \\
& \text{reacting the compound (V) with a compound of the formula (VI):} \\
\end{align*}
\]

\[
\begin{align*}
\text{(VI)} & \\
& \text{or a salt thereof, to give a compound of the formula (VII):}
\end{align*}
\]
removing the carboxyl protecting group $R^5$ to give a compound of the formula (VIII):  

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

wherein $X^2$ is a halogen atom, 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):  

wherein $X^3$ and $X^4$ are a halogen atom, with carbon dioxide, protecting the carboxyl group of the resulting compound of the formula (XII):  

to give a compound of the formula (XIII):  

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

Process B

Among the compounds (I) of the formula (I) wherein R¹ is a substituted or unsubstituted C₁-₆-alkyl group, i.e., the compound of the formula (I-b):

(wherein R¹² is a substituted or unsubstituted C₁-₆-alkyl group) can be prepared by oxidizing a compound of the formula (XVI):

which is obtained by reduction of the compound (IV), to give a compound of the formula (XVII):

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

wherein the symbols are as defined above, reacting the compound (XVIII) with the compound (VI) to give a compound of the formula (XIX):
reacting the compound (XIX) with a metal salt of a compound of the formula (IX-b):

\[ R^{12}\cdot H \]  

(IX-b)

to give a compound of the formula (XX):

followed by oxidizing the compound (XX).

In addition, among the compounds of the formula (I) wherein a group \( R^1 \) is a \( C_{1-6}\)-alkoxy-substituted ethyl group, a morpholino-substituted ethyl group, a 4-(\( C_{1-6}\)-alkyl)piperazinyl group-substituted ethyl group, a 3-pyridylamino-substituted ethyl group, a 2-pyridyl-(\( C_{1-6}\)-alkyl)amino group-substituted ethyl group, a di-(\( C_{1-6}\)-alkyl)aminoethyl group or a hydroxyethyl group, i.e., the compound of the formula (I-c):

\[ \text{CH}_2=\text{CHMgBr} \]  

(XXI)

to give a compound of the formula (XXII):

oxidizing the compound (XXII) to give a compound of the formula (XXIII):
followed by reacting the compound (XXIII) with a compound of the formula (XXIV):

\[ R^6-H \quad (XXIV) \]

**Process C**

[0032] The compound (I-a) can be prepared by reacting a compound of the formula (XXV):

\[ R^8-S \quad (XXV) \]

which is obtained by removing the carboxyl protecting group R^5 of the compound (IV), with the compound (IX-a) to give a compound of the formula (XXVI-a):

\[ R^8-S \quad (XXVI-a) \]

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

\[ R^9SO_{n} \quad (XXVII-a) \]

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

**Process D**

[0033] The compound (I-b) can be prepared by oxidizing a compound of the formula (XXVIII):
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):

followed by reacting the compound (XXVI-b) to give a compound of the formula (XXVII-b):

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):

which is obtained by reacting the dihalogeno compound (XI) with a compound of the formula (XXIX):

R_{12}^{12}.CHO (XXIX)

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

![Chemical Structure](image)

(XXXII)

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

[0035] 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):

![Chemical Structure](image)

(XXXIII)

followed by oxidizing the compound (XXXIII).

Process F

[0036] The compound (I-a) can be prepared by
reacting the compound (XIII) with a compound of the formula (XXXIV):

![Chemical Structure](image)

RSH (XXXIV)

wherein R is a substituted or unsubstituted C₁-₆-alkyl group or a substituted or unsubstituted aryl group, to give a
compound of the formula (XXXV):

![Chemical Structure](image)

(XXXV)

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

![Chemical Structure](image)

(XXXVI)

removing the carboxyl protecting group R⁵ to give a compound of the formula (XXXVII):

![Chemical Structure](image)

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

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, and pyridine, and an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The solvent may be any solvents which do not disturb the reaction, for example, dimethylsulfoxide, tetrahydrofuran, toluene, ethyl acetate, chloroform, dimethoxyethane, xylene or N,N-dimethylformamide. The reaction is carried out at a temperature of -10˚C to room temperature, preferably 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 and peracetic acid, and an inorganic oxidizing agent such as manganese dioxide, sodium periodate, hydrogen peroxide, dinitrogen tetroxide, halogen, hydroperoxide, iodobenzene acetate, t-butyl hypochlorite, sufluryl chloride and potassium peroxymonosulfate. The solvent may be any solvent which does not disturb the reaction, for example, chloroform, methylene chloride, dichloroethane or acetic acid. The reaction is carried out at a temperature of -78˚C to 50˚C, preferably -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 and pyridine, and an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The salt of the compound (VI) is preferably an alkali metal salt such as sodium salt or potassium salt. The solvent may be any solvent which does not disturb the reaction, for example, N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane or dimethylsulfoxide. The reaction is carried out at a temperature of 0˚C to 150˚C, preferably room temperature to 60˚C.

The reaction of removing the protecting group R5 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 or lithium hydroxide, or an alkali metal carbonate such as sodium carbonate or potassium carbonate. The solvent may be 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 0 to 80˚C, preferably 5˚C to 60˚C. The protecting group for a carboxyl group represented by R5 may be any conventional protecting group for a carboxyl group, such as a C1-6-alkyl group or benzyl group.

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 and diethylcyanophosphonate, which is usually used in the peptide synthesis. The base includes, for example, an organic base such as triethylamine and N-methylmorpholine, and the activating agent includes, for example, 1-hydroxybenzotriazole. The solvent may be any solvent which does not disturb the reaction, for example, methylene chloride, tetrahydrofuran, N,N-dimethylformamide, acetonitrile, N,N-dimethylacetamide or ethyl acetate. The reaction is carried out at a temperature of -30˚C to 50˚C, preferably -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 -30˚C to 100˚C, preferably -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 hydroxide, 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 or ethyl acetate. The reaction is carried out at a temperature of -30˚C to 100˚C, preferably -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 or lithium 2,2,6,6-tetramethylpiperidide. The solvent may be any solvent which does not disturb the reaction, for example, N,N-dimethylformamide or tetrahydrofuran. The reaction is carried out at a temperature of 0˚C to 100˚C, preferably 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 (I) with the compound (II). 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 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 or pyridinium dichloromate. The solvent may be any solvent which does not disturb the reaction, for example, chloroform; toluene, ethyl acetate, 1,2-dichloroethane, methylene chloride or tetrahydrofuran. The reaction is carried out at a temperature of 0˚C to 100˚C, preferably room temperature to 70˚C.

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 and lithium hydroxide, and an alkali metal carbonate such as sodium carbonate and potassium carbonate. 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 -20˚C to 80˚C, preferably -5˚C to 60˚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 (XVII) by oxidizing the compound (XVI). The oxidation reaction of the compound (XIX) with a metal salt of the compound (IX-b) to give the compound (XX) may 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 aluminium hydride, and an alkali metal borohydride such as lithium borohydride. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, dioxane, diethyl ether or dimethoxyethane. The reaction is carried out at a temperature of -78˚C to the boiling point of the solvent to be used, preferably -10˚C to room temperature.

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 (XV) with the compound (VI). 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 aluminium hydride, and an alkali metal borohydride such as lithium borohydride. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, dioxane, diethyl ether or dimethoxyethane. The reaction is carried out at a temperature of -78˚C to -30˚C, preferably -100˚C to -70˚C.

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 obtaining the compound (X) by halogenating the compound (XIII) by a halogenating agent.
-78˚C to 60˚C, preferably -78˚C to room temperature.

[0058] 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).

[0059] The reaction of the compound (XXIII) with the compound (XXIV) wherein R6 is a morpholino group, a 4-(C1-6-alkyl)piperazinyl group, a 3-pyridylamino group, a 2-pyrimidyl-(C1-6-alkyl)amino group, or a di-(C1-6-alkyl)amino group to give the compound (I-c) wherein R6 is a morpholino group, a 4-(C1-6-alkyl)piperazinyl group, a 3-pyridylamino group, a 2-pyrimidyl-(C1-6-alkyl)amino group, or a di-(C1-6-alkyl)amino 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 and pyridine, and an inorganic base such as sodium hydroxide, sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The solvent may preferably be ethanol, N,N-dimethyformamide, tetrahydrofuran, dimethoxyethane or dimethylsulfoxide. The reaction may preferably proceed at a temperature of 0˚C to 150˚C, preferably room temperature to 60˚C.

[0060] On the other hand, the reaction of the compound (XXIII) with the compound (XXIV) wherein R6 is a hydroxy group or a C1-6-alkoxy group to give the compound (XXI) wherein R6 is a hydroxy group or a C1-6-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, or an organic acid such as methanesulfonic acid, camphorsulfonic acid, toluenesulfonic acid and benzenesulfonic acid.

[0061] The solvent may preferably be diethyl ether, toluene, benzene, N,N-dimethylformamide, dimethoxyethane or dimethylsulfoxide, The reaction may preferably proceed at a temperature of 0˚C to 150˚C, preferably room temperature to 60˚C.

Process C

[0062] The reaction of removing the protecting group R5 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 R5 for a carboxyl group of the compound (VII).

[0063] 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).

[0064] The reaction of oxidizing the compound (XXVI-a) to give the compound (XXVII-a) can be carried out in the same manner as in the reaction of obtaining the compound (V) by oxidizing the above compound (IV).

[0065] 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

[0066] 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).

[0067] The reaction of oxidizing the compound (XXVIII) to give the 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).

[0068] 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

[0069] 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 and lithium 2,2,6,6-tetramethylpiperidide. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, 1,2-dimethoxyethane or diethyl ether. The reaction is carried out at a temperature of -100˚C to -30˚C, preferably -100˚C to -70˚C.

[0070] 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).

[0071] The reaction of oxidizing 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).

[0072] 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).

[0073] 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**

[0074] 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 and pyridine, or an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The solvent may be any solvent which does not disturb the reaction, for example, N,N-dimethylformamide, tetrahydrofuran, toluene, ethyl acetate, chloroform, dimethoxyethane, xylene or dimethylformamide.

[0075] The reaction is carried out at a temperature of -10˚C to room temperature, preferably 0˚C to room temperature.

[0076] 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).

[0077] 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).

[0078] 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).

[0079] 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. The solvent may be any solvent which does not disturb the reaction, for example, chloroform, methylene chloride, dichloroethane or acetic acid. The reaction is carried out at a temperature of -78˚C to 50˚C, preferably -10˚C to 10˚C.

[0080] 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).

[0081] The compound (I) thus obtained can be converted into a pharmaceutically acceptable salt thereof.

[0082] 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.

[0083] 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**

[0084]

(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-methylsulfinylpyrimidine (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-methylthiopyrimidine (38.34 g), m.p. 86˚C.

(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-hydroxyethyl-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 dimethyl sulfoxide (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

[0085]

(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, and 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 hydroxide carbonation 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+).
EP 1 219 609 B1

(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

[0086]

(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-y1)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).

[0087] 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

[0088]

(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-ethoxycarbonyl-pyrimidine as colorless crystals, 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°C, 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

[0089] 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.
The corresponding starting materials are treated in a similar manner to give the compounds as listed in the following Table 2.

Table 2 (No. 1)

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</table>
Example 22

[0091]

(1) 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 then 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 (210 mg) as a slightly brown crystalline powder, m.p. 139-141˚C, MS (m/z): 191 (M-H).
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-methoxy-benzylamine (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-pyrimidinymethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (87.6 mg), MS (m/z): 484 (MH+).

Examples 23-24

[0092] 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.
Example 25

[0093] 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

[0094] 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-pyridinyl)-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

[0095] 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

[0096] (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+).
The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the
following Table 4.

![Chemical structure](image)

**Table 4 (No. 1)**

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| | | MS(m/z):520(MH<sup>+</sup>)
54 | Cl | | Powder (HCl)  
| | | MS(m/z):537(MH<sup>+</sup>)
55 | Cl | | Amorphous  
| | | MS(m/z):543(MH<sup>+</sup>)
56 | Cl | | M.p.181-183˚C
57 | Cl | | Powder (HCl)  
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| | | MS(m/z):524(MH<sup>+</sup>)
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| | | MS(m/z):522(MH<sup>+</sup>)
63 | Cl | | Amorphous  
| | | MS(m/z):563(MH<sup>+</sup>)
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<td>Powder (HCl) MS(m/z): 543(MH⁺)</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>Cl</td>
<td>M.p. 143-145°C</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>Cl</td>
<td>Powder (HCl) MS(m/z): 504(MH⁺)</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>Cl</td>
<td>M.p. 130°C</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>CN</td>
<td>Powder (HCl) MS(m/z): 474(MH⁺)</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>Cl</td>
<td>Amorphous MS(m/z): 519(MH⁺)</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>CN</td>
<td>Powder (HCl) MS(m/z): 481(MH⁺)</td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>Cl</td>
<td>M.p. 116-119°C</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>Cl</td>
<td>M.p. 159-161°C</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>Cl</td>
<td>Powder (HCl) MS(m/z): 506(MH⁺)</td>
<td></td>
</tr>
</tbody>
</table>
The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the following Table 5.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R⁰</th>
<th>R¹</th>
<th>Physicochemical properties</th>
</tr>
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<tbody>
<tr>
<td>77</td>
<td>Cl</td>
<td></td>
<td>Amorphous MS(m/z):563(MH⁺)</td>
</tr>
<tr>
<td>78</td>
<td>Cl</td>
<td></td>
<td>Powder (HCl) MS(m/z):497(MH⁺)</td>
</tr>
<tr>
<td>79</td>
<td>Cl</td>
<td></td>
<td>M.p.210-214°C</td>
</tr>
<tr>
<td>80</td>
<td>Cl</td>
<td></td>
<td>M.p.149-151.5°C</td>
</tr>
<tr>
<td>81</td>
<td>NO₂</td>
<td></td>
<td>Amorphous MS(m/z):495(MH⁺)</td>
</tr>
<tr>
<td>82</td>
<td>Cl</td>
<td></td>
<td>M.p.215°C</td>
</tr>
<tr>
<td>83</td>
<td>Cl</td>
<td></td>
<td>M.p.151-152°C</td>
</tr>
</tbody>
</table>

Example 84-86

[0099] The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the following Table 5.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R⁰</th>
<th>R¹</th>
<th>Physicochemical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>Cl</td>
<td></td>
<td>Foam MS(m/z):470(MH⁺)</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R¹</th>
<th>Physicochemical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td><img src="image" alt="Structure" /></td>
<td>M.p.177-179°C, MS(m/z):490(MH⁺)</td>
</tr>
<tr>
<td>89</td>
<td><img src="image" alt="Structure" /></td>
<td>M.p.167-169°C, MS(m/z):512(MH⁺)</td>
</tr>
<tr>
<td>90</td>
<td><img src="image" alt="Structure" /></td>
<td>M.p.140.5-141.5°C</td>
</tr>
</tbody>
</table>
Examples 92-145

[0102] The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the following Table 7.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R¹</th>
<th>Physicochemical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td></td>
<td>Amorphous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):527(MH⁺)</td>
</tr>
</tbody>
</table>

Table 7 (No. 1)

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R¹</th>
<th>Physicochemical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>92</td>
<td></td>
<td>Powder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):475(MH⁺)</td>
</tr>
<tr>
<td>93</td>
<td></td>
<td>Powder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):509(MH⁺)</td>
</tr>
<tr>
<td>94</td>
<td></td>
<td>Amorphous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):512(MH⁺)</td>
</tr>
<tr>
<td>95</td>
<td></td>
<td>M.p.150-152°C</td>
</tr>
<tr>
<td>96</td>
<td></td>
<td>M.p.162-163°C</td>
</tr>
<tr>
<td>97</td>
<td></td>
<td>Amorphous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):486(MH⁺)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Physicochemical properties</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>98</td>
<td>![Structure 1]</td>
<td>Amorphous MS(m/z):484(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>99</td>
<td>![Structure 2]</td>
<td>Amorphous MS(m/z):483(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>100</td>
<td>![Structure 3]</td>
<td>Amorphous MS(m/z):497(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>102</td>
<td>![Structure 5]</td>
<td>Amorphous MS(m/z):512(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>105</td>
<td>![Structure 8]</td>
<td>Amorphous MS(m/z):498(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>107</td>
<td>![Structure 10]</td>
<td>M.p.207-208°C</td>
</tr>
<tr>
<td>108</td>
<td>![Structure 11]</td>
<td>Amorphous MS(m/z):547(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Physicochemical properties</td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>109</td>
<td><img src="image1" alt="Compound" /></td>
<td>Amorphous MS(m/z):501(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>110</td>
<td><img src="image2" alt="Compound" /></td>
<td>M.p.172-173°C</td>
</tr>
<tr>
<td>111</td>
<td><img src="image3" alt="Compound" /></td>
<td>M.p.145-147°C</td>
</tr>
<tr>
<td>112</td>
<td><img src="image4" alt="Compound" /></td>
<td>Amorphous MS(m/z):497(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>113</td>
<td><img src="image5" alt="Compound" /></td>
<td>M.p.148-150°C</td>
</tr>
<tr>
<td>114</td>
<td><img src="image6" alt="Compound" /></td>
<td>M.p.217-219°C</td>
</tr>
<tr>
<td>115</td>
<td><img src="image7" alt="Compound" /></td>
<td>Amorphous MS(m/z):484(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>116</td>
<td><img src="image8" alt="Compound" /></td>
<td>Amorphous MS(m/z):514(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>117</td>
<td><img src="image9" alt="Compound" /></td>
<td>Amorphous MS(m/z):568(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>118</td>
<td><img src="image10" alt="Compound" /></td>
<td>M.p.217-220°C</td>
</tr>
<tr>
<td>119</td>
<td><img src="image11" alt="Compound" /></td>
<td>M.p.212-214°C</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R¹</td>
<td>Physicochemical properties</td>
</tr>
<tr>
<td>---------</td>
<td>----</td>
<td>-----------------------------</td>
</tr>
</tbody>
</table>
| 120     | ![Chemical Structure](image1.png) | Amorphous  
MS(m/z):514(MH⁺) |
| 121     | ![Chemical Structure](image2.png) | Amorphous  
MS(m/z):488(MH⁺) |
| 122     | ![Chemical Structure](image3.png) | M.p.142-144°C |
| 123     | ![Chemical Structure](image4.png) | Amorphous  
MS(m/z):472(MH⁺) |
| 124     | ![Chemical Structure](image5.png) | Amorphous  
MS(m/z):497(MH⁺) |
| 125     | ![Chemical Structure](image6.png) | M.p.143-146°C |
| 126     | ![Chemical Structure](image7.png) | Amorphous  
MS(m/z):514(MH⁺) |
| 127     | ![Chemical Structure](image8.png) | Amorphous  
MS(m/z):498(MH⁺) |
| 128     | ![Chemical Structure](image9.png) | Amorphous  
MS(m/z):513(MH⁺) |
<p>| 129     | <img src="image10.png" alt="Chemical Structure" /> | M.p. 101-103°C |
| 130     | <img src="image11.png" alt="Chemical Structure" /> | M.p.215-217°C |
| 131     | <img src="image12.png" alt="Chemical Structure" /> | M.p.180-183°C |</p>
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R¹</th>
<th>Physicochemical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>132</td>
<td></td>
<td>Oil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):482(MH⁺)</td>
</tr>
<tr>
<td>133</td>
<td></td>
<td>M.p.176-179°C</td>
</tr>
<tr>
<td>134</td>
<td></td>
<td>M.p.224-227°C</td>
</tr>
<tr>
<td>135</td>
<td></td>
<td>Amorphous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):500(MH⁺)</td>
</tr>
<tr>
<td>136</td>
<td></td>
<td>M.p.177-180°C</td>
</tr>
<tr>
<td>137</td>
<td></td>
<td>Powder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):486(MH⁺)</td>
</tr>
<tr>
<td>138</td>
<td></td>
<td>Powder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):486(MH⁺)</td>
</tr>
<tr>
<td>139</td>
<td></td>
<td>Powder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):500(MH⁺)</td>
</tr>
<tr>
<td>140</td>
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<td>Amorphous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):499(MH⁺)</td>
</tr>
<tr>
<td>141</td>
<td></td>
<td>Amorphous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):448(MH⁺)</td>
</tr>
<tr>
<td>142</td>
<td></td>
<td>Amorphous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS(m/z):503(MH⁺)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Physicochemical properties</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>143</td>
<td></td>
<td>M.p. 112-114°C</td>
</tr>
<tr>
<td>144</td>
<td></td>
<td>Amorphous, MS(m/z): 512(MH&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>145</td>
<td></td>
<td>M.p. 123-125°C</td>
</tr>
</tbody>
</table>

**Example 146**

[0103] 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<sup>+</sup>).

![Chemical Structure](image1)

**Example 147**

[0104] The corresponding starting compounds are treated in a similar manner to give the compound of the following formula, m.p. 140-144°C.

![Chemical Structure](image2)

**Example 148**

[0105] 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 hydroxide 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 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

[0106]

(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

[0107] 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.
Example 158

[0108]

(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 ml) 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\(^{\circ}\)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\(^{\circ}\)C. The mixture is treated with triethylamine (8.3 ml) 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

[0109] 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.

Claims

1. A compound of the formula (I):

\[
\text{Ring A is a 5- to 10-membered mono- or bicyclic nitrogen-containing heterocycle optionally substituted with C}_{1-6}^{-}\text{alkyl optionally substituted with hydroxy or cyano, formyl, oxo, amino, di(C}_{1-6}^{-}\text{alkyl})amino, hydroxy, C}_{1-6}^{-}\text{alkoxy, C}_{1-6}^{-}\text{alkoxycarbonyl, optionally (C}_{1-6}^{-}\text{alkoxy})-\text{substituted C}_{1-6}^{-}\text{alkanoyl, or pyrimidinyl substituted with (i) benzylamino substituted with a halogen atom and C}_{1-6}^{-}\text{alkoxy and (ii) hydroxy-substituted cycloalkyl-carbamoyl,}}
\]

\[
R^1 \text{ is selected from C}_{1-6}^{-}\text{alkyl optionally substituted with C}_{1-6}^{-}\text{alkoxy, hydroxy, morpholinyl, C}_{1-6}^{-}\text{alkylsulfonyl, di(C}_{1-6}^{-}\text{alkyl})phosphino, di(C}_{1-6}^{-}\text{alkyl})amino, pyrimidinyl-(C}_{1-6}^{-}\text{alkyl})amino, pyridyl, pyridylamino, (C}_{1-6}^{-}\text{alkyl})piperazinyl or pyrimidinyl;}
\]

\[-\text{NH-Q-R}^3, \text{ wherein Q is C}_{1-6}^{-}\text{alkylene or a single bond, and R}^3 \text{ is a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic nitrogen-containing heterocycle optionally substituted with C}_{1-6}^{-}\text{alkyl optionally substituted with hydroxy or cyano, formyl, oxo, amino, di(C}_{1-6}^{-}\text{alkyl})amino, hydroxy, C}_{1-6}^{-}\text{alkoxy, C}_{1-6}^{-}\text{alkoxycarbonyl, optionally (C}_{1-6}^{-}\text{alkoxy})-\text{substituted C}_{1-6}^{-}\text{alkanoyl, or pyrimidinyl substituted with (i) benzylamino substituted with a halogen atom and C}_{1-6}^{-}\text{alkoxy and (ii) hydroxy-substituted cycloalkyl-carbamoyl; and}}
\]

\[-\text{NH-R}^4, \text{ wherein R}^4 \text{ is C}_{3-8}^{-}\text{cycloalkyl optionally substituted with C}_{1-6}^{-}\text{alkoxy, hydroxy, morpholinyl, C}_{1-6}^{-}\text{alkylsulfonyl, di(C}_{1-6}^{-}\text{alkyl})phosphino, di(C}_{1-6}^{-}\text{alkyl})amino, pyrimidinyl-(C}_{1-6}^{-}\text{alkyl})amino, pyridyl, pyridylamino, (C}_{1-6}^{-}\text{alkyl})piperazinyl or pyrimidinyl;}
\]

\[R^2 \text{ is 5- to 10-membered mono- or bicyclic aryl optionally substituted with C}_{1-6}^{-}\text{alkoxy, halogen, cyano, nitro, hydroxy or C}_{1-6}^{-}\text{alkyl; and}}
\]

one of Y and Z is =CH- and the other is =N-; or a pharmaceutically acceptable salt thereof.
2. The compound of claim 1, wherein

Ring A is a nitrogen-containing 5- or 6-membered heteromonocycle or a 8- to 10-membered heterobicycle, each optionally substituted with C<sub>1-6</sub>-alkyl optionally substituted with hydroxy, formyl, amino, hydroxy, C<sub>1-6</sub>-alkoxycarbonyl, or pyrimidinyl substituted with (i) benzylamino substituted with a halogen atom and C<sub>1-6</sub>-alkoxy and (ii) hydroxy-substituted cycloalkylcarbamoyl, R<sup>1</sup> is selected from C<sub>1-6</sub>-alkyl optionally substituted with C<sub>1-6</sub>-alkoxy, hydroxy, morpholinyl, C<sub>1-6</sub>-alkylsulfonfyl, di(C<sub>1-6</sub>-alkyl)phosphino, di(C<sub>1-6</sub>-alkyl)amino, pyrimidinyl-(C<sub>1-6</sub>-alkyl)amino, pyridyl, pyridylamino, or (C<sub>1-6</sub>-alkyl)piperaziny; -NH-Q-R<sup>3</sup>, wherein Q is as defined in claim 1, and R<sup>3</sup> is a nitrogen-containing 5- or 6-membered heteromonocycle or a 8- to 10-membered heterobicycle, each optionally substituted with C<sub>1-6</sub>-alkyl optionally substituted with hydroxy or cyano, oxo, amino, di(C<sub>1-6</sub>-alkyl)amino, or C<sub>1-6</sub>-alkanoyl; and -NH-R<sup>4</sup>, wherein R<sup>4</sup> is C<sub>3-8</sub>-cycloalkyl optionally substituted with C<sub>1-6</sub>-alkoxy, hydroxy, or pyrimidinylxoy; and R<sup>2</sup> is phenyl substituted with C<sub>1-6</sub>-alkoxy, halogen, cyano, nitro, hydroxy or C<sub>1-6</sub>-alkyl.

3. The compound of claim 2, wherein

Ring A is an optionally substituted heterocycle selected from

![Chemical Structures](image)

and

R<sup>3</sup> is an optionally substituted heterocycle selected from

![Chemical Structures](image)
4. The compound of claim 2, wherein
the optional substituent of Ring A is selected from C_{1-6}-alkyl optionally substituted with hydroxy, formyl, and oxo;

R^{1} is selected from
C_{1-6}-alkyl optionally substituted with C_{1-6}-alkoxy or morpholiny;
-NH-Q-R^{3}, wherein R^{3} is a nitrogen-containing 5- or 6-membered heteromonocycle optionally substituted with
C_{1-6}-alkyl; and
-NH-R^{4}, wherein R^{4} is cycloalkyl optionally substituted with C_{1-6}-alkoxy or hydroxy; and
R^{2} is phenyl substituted with C_{1-6}-alkoxy, halogen or cyano.

5. The compound of claim 4, wherein
Ring A is an optionally substituted heterocycle selected from
and

R³ is an optionally substituted heterocycle selected from

6. The compound of claim 1, wherein

Ring A is selected from

R¹ is C₁₋₆-alkyl, (C₁₋₆-alkoxy)C₁₋₆-alkyl, morpholiny1-C₁₋₆-alkyl, a group -NH-Q-R³, wherein R³ is selected from
or a group -NH-R^4, wherein R^4 is

and

R^2 is

7. The compound of claim 4, wherein

R^1 is selected from

(C_1-6-alkoxy)C_1-6-alkyl,
-NH-Q-R^3, wherein R^3 is a nitrogen-containing 5- or 6-membered heteromonocycle optionally substituted with C_1-6-alkyl, and
-NH-R^4, wherein R^4 is hydroxy-substituted cycloalkyl; and

R^2 is phenyl substituted with C_1-6-alkoxy or halogen.

8. The compound of claim 7, wherein

Ring A is an optionally substituted heterocycle selected from:
9. The compound of claim 6, wherein

Ring A is selected from:

and

R³ is an optionally substituted heterocycle selected from:

and

R¹ is (C₁₋₆-alkoxy)C₁₋₆-alkyl, -NH-O-R³, or -NH-R⁴, wherein
R³ is selected from
10. The compound of claim 4, wherein
the optional substituent of Ring A is hydroxy-substituted C_{1-6}-alkyl;
\[ R^1 \] is \(-\text{NH-Q-R}^3 \); and
\[ R^2 \] is phenyl substituted with C_{1-6}-alkoxy or halogen.

11. The compound of claim 10, wherein
Ring A is an optionally substituted heterocycle selected from
12. The compound of claim 9, wherein

Ring A is selected from:

13. The compound according to any one of claims 1-12, wherein Y is =N-, and Z is =CH-.

14. A compound of claim 1, which is selected from

(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-[2(S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;
2-[2(S)-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-(pyridazinylmethyl) carbamoyl] pyrimidine;
2-(4-methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl) carbamoyl]pyrimidine;
(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;
2-[cis,2,5-bis(hydroxymethyl)-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;
2-[cis,2,5-bis(hydroxymethyl)-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;
2-(4-methyl-3-oxo-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-morpholinoethyl) carbamoyl] pyrimidine;
2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl] pyrididine;
(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl] pyrimidine;
(S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-[2-hydroxymethyl-1-pyrroldiny]
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.

16. A compound of claim 1, which is selected from

(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) car-
bamoyl]pyrimidine;
(S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(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.

17. A compound of claim 1, which is selected from

(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) car-
bamoyl]pyrimidine,

or a pharmaceutically acceptable salt thereof.

18. A compound of claim 1, which is selected from

2-(5,6,7,8-Tetrahydro-1,7-naphthyridin-7-yl)-4-(3chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)car-
bamoyl] pyrimidine,

or a pharmaceutically acceptable salt thereof.

19. A compound of claim 1, which is selected from

(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.

20. Pharmaceutical composition comprising as an active ingredient the compound of any of claims 1-19, or a pharma-
21. Use of a compound of one of claims 1-19 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of penile erectile dysfunction.

22. Use of a compound of one of claims 1-19 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of pulmonary hypertension.

23. Use of a compound of one of claims 1-19 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of diabetic gastroparesis.

Patentansprüche

1. Verbindung der Formel (I):

![Chemical Structure](image)

worin

Ring A ein 5- bis 10-gliedriger, mono- oder bicyclischer, stickstoffhaltiger Heterocyclus ist, gegebenenfalls substituiert mit C1-6-Alkyl, das gegebenenfalls mit Hydroxy oder Cyano substituiert ist, Formyl, Oxo, Amino, Di(C1-6-alkyl)amino, Hydroxy, C1-6-Alkoxy, C1-6-Alkoxy carbonyl, gegebenenfalls (C1-6-Alkoxy)-substituiertem C1-6-Alkanoyl, oder Pyrimidinyl, das mit (i) Benzylamino, substituiert mit einem Halogenatom und C1-6-Alkoxy, und (ii) Hydroxy-substituiertem Cycloalkylcarbamoyl substituiert ist, 

R1 ausgewählt ist aus

C1-6-Alkyl, das gegebenenfalls mit C1-6-Alkoxy, Hydroxy, Morpholinyl, C1-6-Alkylsulfonyl, Di(C1-6-alkyl)phosphino, Di(C1-6-alkyl)amino, Pyrimidinyl-(C1-6-alkyl)amino, Pyridyl, Pyridylamino, (C1-6-Alkyl)piperazinyl oder Pyrimidinylxy substituiert ist;

-NH-Q-R3, worin Q C1-6-Alkylen oder eine Einfachbindung ist, und R3 ein 5- oder 6-gliedriger, monocyclischer oder 8- bis 10-gliedriger, bicyclischer, stickstoffhaltiger Heterocyclus ist, gegebenenfalls substituiert mit C1-6-Alkyl, das gegebenenfalls mit Hydroxy oder Cyano substituiert ist, Formyl, Oxo, Amino, Di(C1-6-alkyl)amino, Hydroxy, C1-6-Alkoxy, C1-6-Alkoxy carbonyl, gegebenenfalls (C1-6-Alkoxy)-substituiertem C1-6-Alkanoyl, oder Pyrimidinyl, das mit (i) Benzylamino, substituiert mit einem Halogenatom und C1-6-Alkoxy, und (ii) Hydroxy-substituiertem Cycloalkylcarbamoxy substituiert ist; und

-NH-R4, worin R4 C3-8-Cycloalkyl ist, das gegebenenfalls mit C1-6-Alkoxy, Hydroxy, Morpholinyl, C1-6-Alkylsulfonyl, Di(C1-6-Alkyl)phosphino, Di(C1-6-Alkyl)amino, Pyrimidinyl-(C1-6-alkyl)amino, Pyridyl, Pyridylamino, (C1-6-Alkyl)piperazinyl oder Pyrimidinyloxy substituiert ist;

R2 5- bis 10-gliedriges, mono- oder bicyclisches Aryl ist, das gegebenenfalls mit C1-6-Alkoxy, Halogen, Cyano, Nitro, Hydroxy oder C1-6-Alkyl substituiert ist; und

R1 ausgewählt ist aus
EP 1 219 609 B1

C_{1-6}-Alkyl, das gegebenenfalls mit C_{1-6}-Alkoxy, Hydroxy, Morpholinyl, C_{1-6}-Alkylsulfonyl, Di(C_{1-6}-alkyl)phosphino, Di(C_{1-6}-alkyl)amino, Pyrimidinyl-(C_{1-6}-alkyl)amino, Pyridyl, Pyridylamino oder (C_{1-6}-Alkyl)piperazinyl substituiert ist;

-NH-Q-R^3, worin Q wie in Anspruch 1 definiert ist und R^3 ein stickstoffhaltiger 5- oder 6-gliederiger Heteromonocyclus oder ein 8- bis 10-gliederiger Heterobiclacyclus ist, jeweils gegebenenfalls substituiert mit C_{1-6}-Alkyl, das gegebenenfalls mit Hydroxy oder Cyano substituiert ist, Oxo, Amino, Di(C_{1-6}-alkyl)amino, oder C_{1-6}-Alkanoyl; und

-NH-R^4, worin R^4 C_{3-8}-Cycloalkyl ist, das gegebenenfalls mit C_{1-6}-Alkoxy, Hydroxy oder Pyrimidinylöxy substituiert ist; und

R^2 Phenyl ist, das mit C_{1-6}-Alkoxy, Phenyl, Halogen, Cyano, Nitro, Hydroxy oder C_{1-6}-Alkyl substituiert ist.

3. Verbindung gemäss Anspruch 2, worin
Ring A ein gegebenenfalls substituierter Heterocycclus ist, ausgewählt aus:

und
R^3 ein gegebenenfalls substituierter Heterocycclus ist, ausgewählt aus:
4. Verbindung gemäß Anspruch 2, worin:

   der optionale Substituent von Ring A ausgewählt ist aus C_{1-6}-Alkyl, das gegebenenfalls mit Hydroxy substituiert ist, Formyl und Oxo;
   R^1 ausgewählt ist aus:
   C_{1-6}-Alkyl, das gegebenenfalls mit C_{1-6}-Alkoxy oder Morpholiny1 substituiert ist;
   -NH-Q-R^3, worin R^3 ein stickstoffhaltiger, 5- oder 6-gliedriger Heteromonocyclus ist, der gegebenenfalls mit C_{1-6}-Alkyl substituiert ist; und
   -NH-R^4, worin R^4 Cycloalkyl ist, das gegebenenfalls mit C_{1-6}-Alkoxy oder Hydroxy substituiert ist; und
   R^2 Phenyl ist, das mit C_{1-6}-Alkoxy, Halogen oder Cyano substituiert ist.

5. Verbindung gemäß Anspruch 4, worin:
Ring A ein gegebenenfalls substituierter Heterocyclus ist, ausgewählt aus:

und

und

R³ ein gegebenenfalls substituierter Heterocyclus ist, ausgewählt aus:

6. Verbindung gemäß Anspruch 1, worin:

Ring A ausgewählt ist aus:
R\textsuperscript{1} C\textsubscript{1-6}-Alkyl, (C\textsubscript{1-6}-Alkoxy)-C\textsubscript{1-6}-alkyl, Morpholinyl-C\textsubscript{1-6}-alkyl, eine Gruppe -NH-Q-R\textsuperscript{3}, worin R\textsuperscript{3} ausgewählt ist aus:

oder eine Gruppe -NH-R\textsuperscript{4} ist, worin R\textsuperscript{4}
7. Verbindung gemäß Anspruch 4, worin
   R¹ ausgewählt ist aus:
   - (C₁₋₆-Alkoxy)-C₁₋₆-alkyl,
   - -NH-Q-R³, worin R³ ein stickstoffhaltiger, 5- oder 6-gliedriger Heteromonocyclus ist, der gegebenenfalls mit
     C₁₋₆-Alkyl substituiert ist, und
   - -NH-R⁴, worin R⁴ Hydroxy-substituiertes Cycloalkyl ist; und
   R² mit C₁₋₆-Alkoxy oder Halogen substituiertes Phenyl ist.

8. Verbindung gemäß Anspruch 7, worin:
   Ring A ein gegebenenfalls substituierter Heterocyclus ist, ausgewählt aus:

   und

   R³ ein gegebenenfalls substituierter Heterocyclus ist, ausgewählt aus:
9. Verbindung gemäß Anspruch 6, worin:

Ring A ausgewählt ist aus:

R¹ (C₁₋₆-Alkoxy)C₁₋₆-alkyl, -NH-Q-R³ oder -NH-R⁴ ist, worin:

R³ ausgewählt ist aus:
ist; und
R²

10. Verbindung gemäß Anspruch 4, worin:
der gegebenenfalls vorhandene Substituent von Ring A Hydroxy-substituierter C₁₋₆-Alkyl ist;
R¹ -NH-Q-R³ ist; und
R² mit C₁₋₆-Alkoxy oder Halogen substituiertes Phenyl ist.

11. Verbindung gemäß Anspruch 10, worin:
Ring A ein gegebenenfalls substituierter Heterocyclus ist, ausgewählt aus:

12. Verbindung gemäß Anspruch 9, worin:
Ring A ausgewählt ist aus:
und R₁ -NH-Q-R₃ ist, worin R₃ ausgewählt ist aus:

und R₂ ist.

13. Verbindung gemäss irgendeinem der Ansprüche 1 bis 12, worin Y =N- und Z =CH- ist.

14. Verbindung gemäss Anspruch 1, ausgewählt aus

(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)-carbamoyl]pyrimidin;
2-(6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin;
2-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(trans-4-methoxy-cyclohexyl)carbamoyl]pyrimidin;
2-(6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidin;
2-(6,7-Dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidin;
(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidin;
(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidin;
2-(4-Methyl-3-oxo-1-piperazinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carba-
moyl]pyrimidin; 2-(4-Formyl-1-piperazinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidin; 2-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidin; 2-[cis-2,5-bis(hydroxymethyl)-1-pyrrolidinyl]-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin; 2-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin; 2-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidin; 2-(5,6,7,8-Tetrahydro-1,7-naphthydrin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-acetylpyrimidin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(4-pyridazinylmethyl)carbamoyl]pyrimidin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrazin; 2-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidin; oder ein pharmazeutisch annehmbares Salz hiervon.

15. Verbindung gemäß Anspruch 1, ausgewählt aus

(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidin; 2-(4-Methyl-3-oxo-1-piperazinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidin; 2-(4-Formyl-1-piperazinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidin; 2-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin; 2-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidin; 2-(5,6,7,8-Tetrahydro-1,7-naphthydrin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrazin; (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidin;
midin;
(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidin,
oder ein pharmazeutisch annehmbares Salz hiervon.

16. Verbindung gemäss Anspruch 1, ausgewählt aus
(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin;
(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidin;
2-(5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin;
2-(5,6,7,8-Tetrahydro-1,7-naphthydrin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidin;
(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidin;
(S)-2-[N-(2-Pyrimidinylmethyl)carbamoyl]-3-(3-chlor-4-methoxybenzylamino)-5-[2-hydroxymethyl-1-pyrollidinyl]pyrazin;
(S)-2-[N-(2-Morpholinoethyl)carbamoyl]-3-(3-chlor-4-methoxybenzylamino)-5-[2-hydroxymethyl-1-pyrollidinyl]pyrazin;
(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidin,
oder ein pharmazeutisch annehmbares Salz hiervon.

17. Verbindung gemäss Anspruch 1, ausgewählt aus
(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidin,
oder ein pharmazeutisch annehmbares Salz hiervon.

18. Verbindung gemäss Anspruch 1, ausgewählt aus
2-(5,6,7,8-Tetrahydro-1,7-naphthydrin-7-yl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidin,
odern ein pharmazeutisch annehmbares Salz hiervon.

19. Verbindung gemäss Anspruch 1, ausgewählt aus
(S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chlor-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidin,
oder ein pharmazeutisch annehmbares Salz hiervon.

20. Pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäss einem der Ansprüche 1 bis 19 oder ein pharmazeutisch annehmbares Salz hiervon als Wirkstoff.


22. Verwendung einer Verbindung gemäss einem der Ansprüche 1 bis 19 oder eines pharmazeutisch annehmbaren Salzes hiervon zur Herstellung eines Medikaments zur Behandlung von pulmonaler Hypertonie.

23. Verwendung einer Verbindung gemäss einem der Ansprüche 1 bis 19 oder eines pharmazeutisch annehmbaren
Revendications

1. Composé de formule (I):

\[
\text{dans laquelle}
\]

le cycle A est un hétérocycle contenant de l’azote mono- ou bicyclique de 5 à 10 chaînons éventuellement substitué par un groupe alkyle en C_{1-6} éventuellement substitué par un groupe hydroxy ou cyano, formyle, oxo, amino, di(alkyl en C_{1-6})amino, hydroxy, alcoxy en C_{1-6}, alcoxy carbonyle en C_{1-6}, alcanoyle en C_{1-6} éventuellement (alcoxy en C_{1-6})-substitué, ou pyrimidinyle substitué par (i) un groupe benzylamino substitué par un atome d’halogène et un groupe alcoxy en C_{1-6} et (ii) un groupe cycloalkylcarbamoyle hydroxy-substitué, R^1 est choisi parmi un groupe alkyle en C_{1-6} éventuellement substitué par un groupe alcoxy en C_{1-6}, hydroxy, morpholinyle, alkylsulfonyle en C_{1-6}, di(alkyl en C_{1-6})phosphino, di(alkyl en C_{1-6})amino, pyrimidinyl-(alkyl en C_{1-6})-amino, pyridyle, pyridylamino, (alkyl en C_{1-6})pipérazinyne ou pyrimidinyloxy ; -NH-Q-R^3, où Q est un groupe alkylène en C_{1-6} ou une liaison unique, et R^3 est un hétérocycle contenant de l’azote monocyclique à 5 ou 6 chaînons ou bicyclique à 8 à 10 chaînons éventuellement substitué par un groupe alkyène en C_{1-6} éventuellement substitué par un groupe hydroxy ou cyano, formyle, oxo, amino, di(alkyl en C_{1-6})amino, hydroxy, alcoxy en C_{1-6}, alcoxy carbonyle en C_{1-6}, alcanoyle en C_{1-6} éventuellement alcoxy en C_{1-6}-substitué, ou pyrimidinyle substitué par (i) un groupe benzylamino substitué par un atome d’halogène et un groupe alcoxy en C_{1-6} et (ii) un groupe cycloalkylcarbamoyle hydroxy-substitué ; et -NH-R^4, où R^4 est un groupe cycloalkyle en C_{3-8} éventuellement substitué par un groupe alcoxy en C_{1-6}, hydroxy, morpholinyle, alkylsulfonyle en C_{1-6}, di(alkyl en C_{1-6})phosphino, di(alkyl en C_{1-6})amino, pyrimidinyl-(alkyl en C_{1-6})-amino, pyridyle, pyridylamino, (alkyl en C_{1-6})pipérazinyne ou pyrimidinyloxy ; R^2 est un groupe aryle mono- ou bicyclique de 5 à 10 chaînons éventuellement substitué par un groupe alcoxy en C_{1-6}, un hétérogène, un groupe cyani, nitro, hydroxy ou alkyène en C_{1-6} ;

ou un sel de celui-ci acceptable du point de vue pharmaceutique.

2. Composé selon la revendication 1, dans lequel

le cycle A est un hétéromonocycle à 5 ou 6 chaînons ou un hétérobicycle de 8 à 10 chaînons contenant de l’azote, chacun éventuellement substitué par un groupe alkyène en C_{1-6} éventuellement substitué par un groupe hydroxy, formyle, oxo, amino, hydroxy, alcoxy carbonyle en C_{1-6}, ou pyrimidinyle substitué par (i) un groupe benzylamino substitué par un atome d’halogène et un groupe alcoxy en C_{1-6} et (ii) un groupe cycloalkylcarbamoyle hydroxy-substitué, R^1 est choisi parmi un groupe alkyène en C_{1-6} éventuellement substitué par un groupe alcoxy en C_{1-6}, hydroxy, morpholinyle, alkylsulfonyle en C_{1-6}, di(alkyl en C_{1-6})phosphino, di(alkyl en C_{1-6})amino, pyrimidinyl-(alkyl en C_{1-6})-amino, pyridyle, pyridylamino, ou (alkyl en C_{1-6})pipérazinyne ; -NH-Q-R^3, où Q est tel que défini dans la revendication 1, et R^3 est un hétéromonocycle à 5 ou 6 chaînons ou hétérobicycle à 8 à 10 chaînons contenant de l’azote, chacun éventuellement substitué par un groupe alkyène en C_{1-6} éventuellement substitué par un groupe hydroxy ou cyano, oxo, amino, di(alkyl en C_{1-6})amino, ou alcanoyle en C_{1-6} ; -NH-R^4, où R^4 est un groupe cycloalkyl en C_{3-8} éventuellement substitué par un groupe alcoxy en C_{1-6}, hydroxy, ou pyrimidinyloxy ; R^2 est un groupe phényle substitué par un groupe alcoxy en C_{1-6}, un hétérogène, un groupe cyano, nitro, hydroxy ou alkyène en C_{1-6}.
3. Composé selon la revendication 2, dans lequel
le cycle A est un hétérocycle éventuellement substitué choisi parmi

, et
R₃ est un hétérocycle éventuellement substitué choisi parmi
4. Composé selon la revendication 2, dans lequel
le substituant optionnel du cycle A est choisi parmi
un groupe alkyle en C\textsubscript{1-6} éventuellement substitué par un groupe hydroxy, formyle, et oxo ;
R\textsuperscript{1} est choisi parmi
un groupe alkyle en C\textsubscript{1-6} éventuellement substitué par un groupe alcoxy en C\textsubscript{1-6} ou morpholinyle ; -NH-Q-R\textsubscript{3}, où
R\textsuperscript{3} est un hétéromonocycle contenant de l’azote à 5 ou 6 chaînons éventuellement substitué par un groupe alkyle en C\textsubscript{1-6} ; et -NH-R\textsubscript{4}, où R\textsuperscript{4} est un groupe cycloalkyle éventuellement substitué par un groupe alcoxy en C\textsubscript{1-6} ou hydroxy ; et
R\textsuperscript{2} est un groupe phényle substitué par un groupe alcoxy en C\textsubscript{1-6}, un halogène ou un groupe cyano.

5. Composé selon la revendication 4, dans lequel
le cycle A est un hétérocycle éventuellement substitué choisi parmi
et

R$^3$ est un hétérocycle éventuellement substitué choisi parmi

6. Composé selon la revendication 1, dans lequel le cycle A est choisi parmi

R$^1$ est un groupe alkyle en C$_{1-6}$, (alcoxy en C$_{1-6}$)alkyle en C$_{1-6}$, morpholiny-alkyle en C$_{1-6}$, un groupe -NH-Q-R$^3$, dans lequel R$^3$ est choisi parmi
ou un groupe \(-\text{NH-R}^4\), dans lequel \(\text{R}^4\) est

\[
\begin{align*}
\text{R}^1 & \quad \text{choisi parmi un groupe } (\text{alcoxy en } C_{1-6})\text{alkyle en } C_{1-6}, \\
\text{R}^2 & \quad \text{un groupe phényle substitué par un groupe alcoxy en } C_{1-6} \text{ ou un halogène.}
\end{align*}
\]
9. Composé selon la revendication 6, dans lequel le cycle A est choisi parmi:

; et $R^1$ est un groupe (alcoxy en C$_{1-6}$)alkyle en C$_{1-6}$-NH-$Q$-$R^3$, ou -NH-$R^4$, dans lequel $R^3$ est choisi parmi
et $R^4$ est 

le substituant optionnel du cycle A est le groupe alkyle en C1-6 à substitution hydroxy ; 
R$^1$ est, -NH-Q-R$^3$; et 
R$^2$ est un groupe phényle substitué par un groupe alcoxy en C1-6 ou par un halogène.

11. Composé selon la revendication 10, dans lequel 
le cycle A est un hétérocycle éventuellement substitué choisi parmi
; et $R^3$ est un hétérocyle éventuellement substitué choisi parmi

12. Composé selon la revendication 9, dans lequel le cycle A est choisi parmi

et

et $R^1$ est un groupe $-NH-Q-R^3$ dans lequel $R^3$ est choisi parmi

et

et $R^2$ est

13. Composé selon l'une quelconque des revendications 1 à 12, dans lequel Y est $=N-$ et Z est $=CH-$.

14. Composé selon la revendication 1, qui est choisi parmi les

(S)-2-[(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-pyrimidinylméthyl)carbamoyl]pyrimidine ;

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

2-(5,6,7,8-tétrahydroimidazolo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(trans-4-méthoxy-cyclohexyl)carbamoyl]-pyrimidine ;
2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-méthoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine ;
2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(4-pyrimidinylméthyl)carbamoyl]pyrimidine ;
(2-4-méthyl-3-oxo-1-pipérazinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine ;
2-(4-formyl-1-pipérazinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine ;
2-(5,6,7,8-tétrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine ;
2-[(2S)-2-hydroxyméthyl-1-pyrrolidinyl]-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(4-pyridazinylméthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(5-pyrimidinylméthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-pyridylméthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine ;
(S)-2-[N-(2-pyrimidinylméthyl)carbamoyl]-3-(3-chloro-4-méthoxybenzylamino)-5-(2-hydroxyméthyl-1-pyrrolidinyl)pyrazine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine ;
2-(5,6,7,8-tétrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(1,3,5-triméthyl-4-pyrazolyl)carbamoyl]pyrimidine ;
2-(4-formyl-1-pipérazinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine ;
ou un sel de ceux-ci acceptable du point de vue pharmaceutique.

15. Composé selon la revendication 1, qui est choisi parmi les
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-pyrimidinylméthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(4-pyrimidinylméthyl)carbamoyl]pyrimidine ;
2-(4-méthyl-3-oxo-1-pipérazinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine ;
2-(4-formyl-1-pipérazinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine ;
2-(5,6,7,8-tétrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-pyrimidinylméthyl)carbamoyl]pyrimidine ;
2-(5,6,7,8-tétrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine ;
2-(5,6,7,8-tétrahydro-1,7-naphtyridin-7-yl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(5-pyrimidinylméthyl)carbamoyl]pyrimidine ;
(S)-2-[N-(2-pyrimidinylméthyl)carbamoyl]-3-(3-chloro-4-méthoxybenzylamino)-5-[2-hydroxyméthyl-1-pyrrolidinyl]pyrazine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[[2-méthoxyéthyl]carbonyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(1,3,5-triméthyl-4-pyrazolyl)carbamoyl]pyrimidine,
ou un sel de ceux-ci acceptable du point de vue pharmaceutique.

16. Composé selon la revendication 1, qui est choisi parmi les
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-pyrimidinylméthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine ;
2-(5,6,7,8-tétrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-pyrimidinylméthyl)carbamoyl]pyrimidine ;
2-(5,6,7,8-tétrahydro-1,7-naphtyridin-7-yl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine ;
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(1,3,5-triméthyl-4-pyrazolyl)carbamoyl]pyrimidine,
ou un sel de ceux-ci acceptable du point de vue pharmaceutique.

17. Composé selon la revendication 1, qui est choisi parmi la
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-pyrimidinylméthyl)carbamoyl]pyrimidine,
ou un sel de celle-ci acceptable du point de vue pharmaceutique.

18. Composé selon la revendication 1, qui est choisi parmi la
2-(5,6,7,8-tétrahydro-1,7-naphtyridin-7-yl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(2-morpholinoéthyl)carbamoyl]pyrimidine,
ou un sel de celle-ci acceptable du point de vue pharmaceutique.

19. Composé selon la revendication 1, qui est choisi parmi la
(S)-2-(2-hydroxyméthyl-1-pyrrolidinyl)-4-(3-chloro-4-méthoxybenzylamino)-5-[N-(1,3,5-triméthyl-4-pyrazolyl)carbamoyl]pyrimidine,
ou un sel de celle-ci acceptable du point de vue pharmaceutique.

20. Composition pharmaceutique comprenant comme ingrédient actif le composé selon l’une quelconque des revendications 1 à 19, ou un sel de celui-ci acceptable du point de vue pharmaceutique.


22. Utilisation d’un composé selon l’une quelconque des revendications 1 à 19 ou d’un sel de celui-ci acceptable du
point de vue pharmaceutique, pour la fabrication d'un médicament pour le traitement de l'hypertension pulmonaire.

23. Utilisation d'un composé selon l'une quelconque des revendications 1 à 19 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, pour la fabrication d'un médicament pour le traitement de la gastroparèse diabétique.