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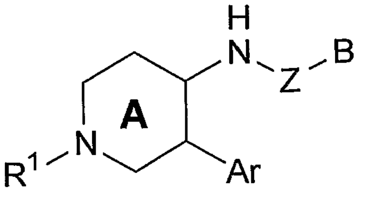
(54) Title: PIPERIDINE DERIVATIVES AS TACHYKININ RECEPTOR ANTAGONISTS



(I)

(57) **Abstract:** A novel piperidine derivative represented by the formula (I) (I) wherein Ar is a phenyl group optionally having substituent(s), R¿1? is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s), Z is a methylene group optionally having C?1-6#191 alkyl group(s), ring A is a piperidine ring optionally further having substituent(s), and B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring), or a salt thereof has a superior tachykinin receptor antagonistic action and the like, and is useful as an agent for the prophylaxis or treatment of lower urinary tract disease and the like.

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DESCRIPTION

PIPERIDINE DERIVATIVES AS TACHYKININ RECEPTOR ANTAGONISTS

Technical Field

The present invention relates to a novel piperidine derivative having excellent antagonistic action for a tachykinin receptor, and use thereof.

Background of the Invention

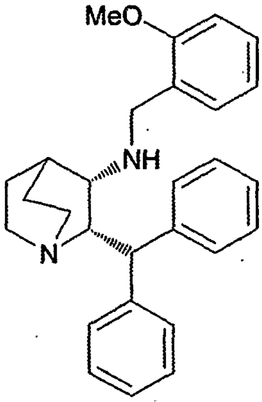
Tachykinin is a generic term for a group of neuropeptides. Substance P (SP), neurokinin-A and neurokinin-B are known in mammals, and these peptides are known to bind to the corresponding receptors (neurokinin-1, neurokinin-2 and neurokinin-3) that exist in a living body and thereby to exhibit various biological activities.

Of such neuropeptides, SP has the longest history and has been studied in detail. In 1931, the existence of SP in the extract from equine intestines was confirmed, and in 1971, its structure was determined. SP is a peptide consisting of 11 amino acids.

SP is broadly distributed over the central and peripheral nervous systems, and has various physiological activities such as vasodilation, enhancement of vascular extravasation, contraction of smooth muscles, excitation of neurons, salivation, enhancement of diuresis, immunological enhancement and the like, in addition to the function as a transmitter substance for primary sensory neurons. In particular, it is known that SP released from the terminal in the spinal (dorsal) horn due to a pain impulse transmits the information of pain to secondary neurons, and that SP released from the peripheral terminal induces an inflammatory response in the receptor thereof. Thus, it is considered that SP is involved in various disorders (e.g., pain, headache, particularly migraine, Alzheimer's disease, multiple sclerosis, cardiovascular modulation, chronic inflammatory diseases such as chronic rheumatic arthritis, respiratory diseases including asthma or allergic rhinitis, intestinal inflammatory diseases including ulcerative colitis and Crohn's disease, ocular damage and ocular inflammatory diseases, proliferative vitreous retinopathy, irritable bowel syndrome, urinary frequency, psychosis, vomiting, etc.) [see a review article: Physiological Reviews, Vol. 73, pp. 229-308 (1993); Journal of Autonomic Pharmacology, Vol. 13, pp. 23-93 (1993)].

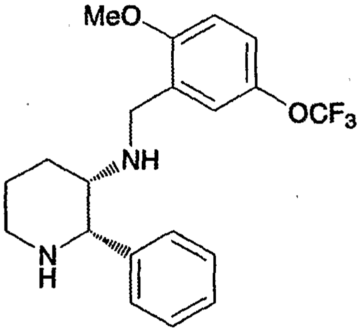
At present, the following compounds have been known as those having antagonistic actions for SP receptors.

In EP-A-436,334, disclosed are the compound of the formula:

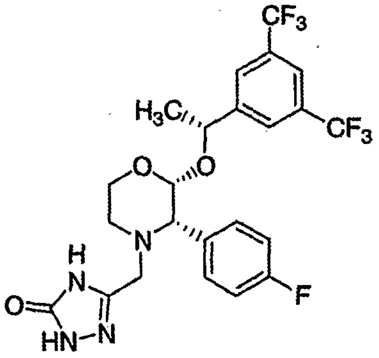


, and the like,

in WO 92/17449, disclosed are the compound of the formula:

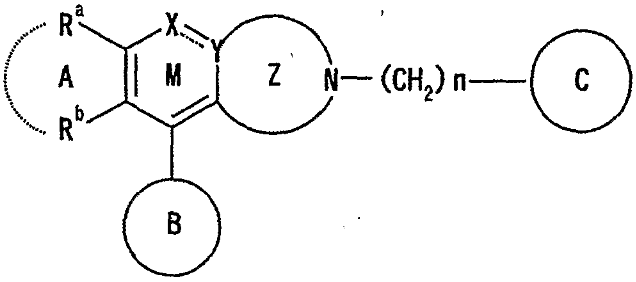


, and the like, in WO 95/16679, disclosed are the compound of the formula:



, and the like, and

in JP-A-9-263585, disclosed are the heterocyclic compounds represented by the formula:

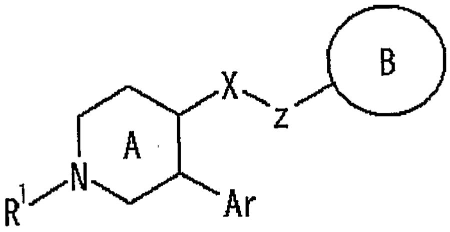


wherein Ring M is a heterocycle having -N=C<, -CO-N< or -CS-N< as a partial structure of

$$-X \mathrel{\substack{\text{---}\\ \text{- - -}}} Y < \;;$$

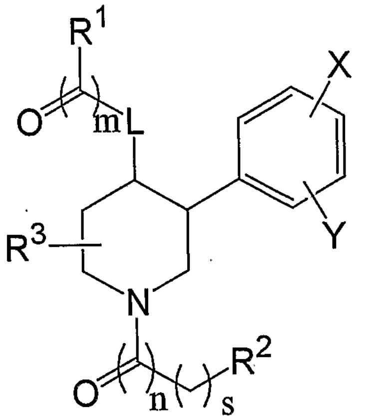
R^a and R^b are bonded to each other to form ring A, or they are the same or different and represent a hydrogen atom or a substituent in Ring M; ring A and B are homocyclic or heterocyclic rings optionally having substituent(s), respectively and at least one of them is a heterocyclic ring optionally having substituent(s); Ring C is a homocyclic or heterocyclic ring optionally having substituent(s); Ring Z is a nitrogen-containing heterocyclic ring optionally having substituent(s); and n is an integer of 1 to 6, or salts thereof, and the like.

WO03/101964 describes a compound having a tachykinin receptor antagonistic action, which is represented by the formula:



wherein Ar is an aryl group, an aralkyl group or an aromatic heterocyclic group, each of which optionally having substituent(s), R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s), X is an oxygen atom or an imino group optionally having a substituent, Z is a methylene group optionally having substituent(s), ring A is a piperidine ring optionally further having substituent(s), ring B is an aromatic ring optionally having substituent(s), provided when Z is a methylene group substituted by an oxo group, then R^1 is not a methyl group and when Z is a methylene group substituted by a methyl group, then B is an aromatic ring having substituent(s), or a salt thereof.

US 2005/0256164 A describes a compound having a tachykinin receptor antagonistic action, which is represented by the formula:



wherein m is 0 or 1; n is 0 or 1; s is 0 or 1; L is -O- or -N(R^4)-; R^1 and R^2 are each independently hydrogen atom, aryl, heteroaryl, C_{1-6} alkyl, heterocyloalkyl, C_{1-6} alkylheterocycloalkyl, C_{1-6} alkylheteroaryl, C_{1-6} alkyl-O-aryl, C_{1-6} alkylaryl, and -$CH_2N(R^4)(R^5)$, wherein each of said heterocyloalkyl, C_{1-6} alkylheterocycloalkyl, C_{1-6} alkylheteroaryl, C_{1-6} alkyl-O-aryl, aryl, C_{1-6} alkylaryl, heteroaryl and -$CH_2N(R^4)(R^5)$ is optionally substituted with 1 to 3 substituents independently selected from X', Y' and Z'; R^3 is hydrogen atom, CF_3, OH, or C_{1-6} alkyl; R^4 and R^5 are each independently selected from hydrogen atom, C_{1-6} alkyl, or $C_{1-6}(C{=}O)R^7$; R^7 is C_{1-6} alkyl, OH, -$N(R^4)(R^5)$ or -OR^4; R^8 and R^9 are each independently C_{1-6} alkyl; X, Y, X', Y' and Z' are each independently selected from hydrogen atom, C_{1-6} alkyl, C_{1-6} alkyl-NR^4R^5, CF_3, OH, -O-C_{1-6} alkyl, C_{1-6} alkyl-$(C{=}O)R^7$, aryl, heteroaryl, cycloalkyl, -NO_2, C_{1-6} alkylaryl, -O-aryl, halogen, CN, -$CH_3N(R^4)(R^5)$, -$(C{=}O)R^7$, -$R^6(C{=}O)R^7$ or -$R^6(C{=}O)N(R^4)(R^5)$; and R^6 is a bond, -CH_2-, -O-, or -NR^4-, or a salt thereof.

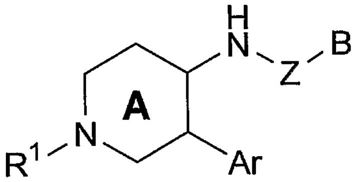
Disclosure of the Invention

An object of the present invention is to provide a piperidine derivative having antagonistic action for a tachykinin receptor, etc. with a different chemical structure from the known compounds including the above-mentioned compounds, an agent for the prophylaxis or treatment of lower urinary tract diseases comprising the compound, and the like.

The present inventors have made extensive studies in consideration of the above-mentioned situation and, as a result, have found unexpectedly that piperidine derivatives represented by the formula (I) below or a salt thereof have excellent antagonistic action for a tachykinin receptor (particularly antagonistic action for a SP receptor) as based on their peculiar chemical structures and are sufficiently satisfactory as pharmaceutical compositions. On the basis of these findings, the present inventors have completed the present invention.

Specifically, the present invention relates to:

[1] a compound represented by the formula (I):



(I)

wherein

Ar is a phenyl group optionally having substituent(s),

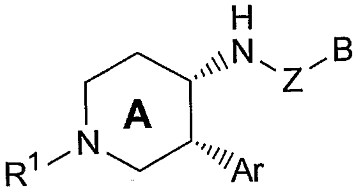
R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),

Z is a methylene group optionally having C_{1-6} alkyl group(s),

ring A is a piperidine ring optionally further having substituent(s), and

B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring) or a salt thereof;

[2] the compound of the above-mentioned [1], which is an optically active form represented by the formula (I-a)


(I-a)

wherein each symbol is as defined in the above-mentioned [1];

[3] the compound of the above-mentioned [1], wherein Ar is a phenyl group;

[4] the compound of the above-mentioned [1], wherein R^1 is a hydrogen atom or an acyl group;

[5] the compound of the above-mentioned [1], wherein R^1 is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl-carbonylamino group, (b) a 5- or 6-membered nitrogen-containing heterocyclic group optionally having 1 to 4 substituents selected from the group consisting of a C_{1-6} alkyl group and an oxo group, (c) a carbamoyl group, (d) a hydroxy group and (e) a C_{1-6} alkylsulfonyl group,

(3) a C_{1-6} alkoxy-carbonyl group,

(4) a C_{3-6} cycloalkyl-carbonyl group optionally having carbamoyl group(s),

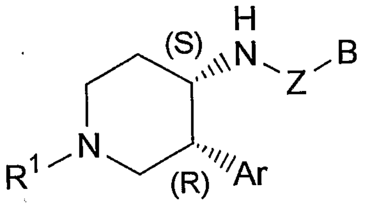
(5) a 5- or 6-membered nitrogen-containing heterocycle-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) an oxo group and (c) C_{1-6} alkyl-carbonyl group optionally having hydroxy group(s), or

(6) a mono-C_{1-6} alkyl-carbamoyl group;

[6] the compound of the above-mentioned [1], wherein Z is a methylene group;

[7] the compound of the above-mentioned [1], wherein ring A is a piperidine ring without further substituent(s);

[8] the compound of the above-mentioned [1], which is an optically active form represented by the formula (I-b)



(I-b)

wherein each symbol is as defined in the above-mentioned [1];

[9] the compound of the above-mentioned [1], wherein B is a nitrogen-containing aromatic heterocyclic group optionally having substituent(s);

[10] the compound of the above-mentioned [1], wherein B is (1) a pyridyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-6} alkyl group, (c) a hydroxy group, (d) a C_{1-6} alkoxy group, (e) a C_{6-10} aryl group optionally having cyano group(s) and (f) a nitrogen-containing aromatic heterocyclic group optionally substituted by C_{1-6} alkyl group(s) optionally having halogen atom(s),

(2) a pyrimidyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) a C_{1-6} alkoxy group optionally having halogen atom(s) and (c) a C_{3-6} cycloalkyl group,

(3) a pyrazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group optionally having halogen atom(s) or

(4) a thiazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group;

[11] the compound of the above-mentioned [1], wherein Ar is a phenyl group,

R^1 is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl-carbonylamino group, (b) a 5- or 6-membered nitrogen-containing heterocyclic group optionally having 1 to 4 substituents selected from the group consisting of a C_{1-6} alkyl group and an oxo group, (c) a carbamoyl group, (d) a hydroxy group and (e) a C_{1-6} alkylsulfonyl group,

(3) a C_{1-6} alkoxy-carbonyl group,

(4) a C_{3-6} cycloalkyl-carbonyl group optionally having carbamoyl group(s),

(5) a 5- or 6-membered nitrogen-containing heterocycle-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) an oxo group and (c) a C_{1-6} alkyl-carbonyl group optionally having hydroxy group(s), or

(6) a mono-C_{1-6} alkyl-carbamoyl group,

Z is a methylene group,

ring A is a piperidine ring without further substituent(s), and

B is (1) a pyridyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-6} alkyl group, (c) a hydroxy group, (d) a C_{1-6} alkoxy group, (e) a C_{6-10} aryl group optionally having cyano group(s) and (f) a nitrogen-containing aromatic heterocyclic group optionally substituted by C_{1-6} alkyl group(s) optionally having halogen atom(s),

(2) a pyrimidyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) a C_{1-6} alkoxy group optionally having halogen atom(s) and (c) a C_{3-6} cycloalkyl group,

(3) a pyrazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a)

a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group optionally having halogen atom(s) or

(4) a thiazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group;

[12] N-{2-[(3R,4S)-4-({[5-(4-cyanophenyl)-2-methoxypyridin-3-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide,

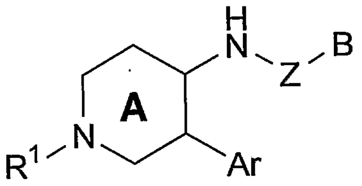
N-(2-{(3R,4S)-4-[({2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]pyridin-3-yl}methyl)amino]-3-phenylpiperidin-1-yl}-2-oxoethyl)acetamide,

N-[2-((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide, or

N-{2-[(3R,4S)-4-({[1-(4-bromophenyl)-3-methoxy-1H-pyrazol-4-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide,

or a salt thereof ;

[13] a prodrug of a compound represented by the formula (I):


(I)

wherein

Ar is a phenyl group optionally having substituent(s),

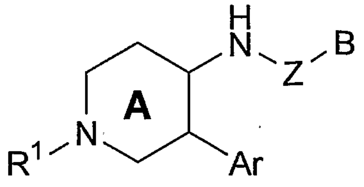
R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),

Z is a methylene group optionally having C_{1-6} alkyl group(s),

ring A is a piperidine ring optionally further having substituent(s), and

B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring) or a salt thereof;

[14] a pharmaceutical composition comprising a compound represented by the formula (I):



(I)

wherein

Ar is a phenyl group optionally having substituent(s),

R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),

Z is a methylene group optionally having C_{1-6} alkyl group(s),

ring A is a piperidine ring optionally further having substituent(s), and

B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring) or a salt thereof, or a prodrug thereof and a pharmaceutically acceptable carrier;

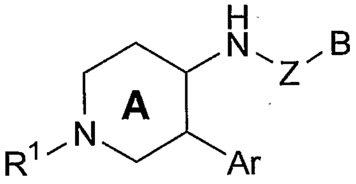
[15] the pharmaceutical composition of the above-mentioned [14], which is a tachykinin receptor antagonist;

[16] the pharmaceutical composition of the above-mentioned [14], which is an agent for the prophylaxis or treatment of lower urinary tract disease, gastrointestinal disease or central nervous system disease;

[17] the pharmaceutical composition of the above-mentioned [14], which is an agent for the prophylaxis or treatment of overactive bladder, irritable bowel syndrome, inflammatory bowel disease, vomiting, nausea, depression, anxiety neurosis, anxiety, pelvic visceral

pain or interstitial cystitis;

[18] a method for the prophylaxis or treatment of lower urinary tract disease, gastrointestinal disease or central nervous system disease in a mammal, which comprises administering an effective amount of a compound represented by the formula (I):

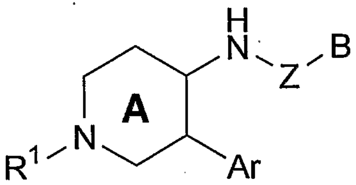


(I)

wherein

Ar is a phenyl group optionally having substituent(s),
R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),
Z is a methylene group optionally having C_{1-6} alkyl group(s),
ring A is a piperidine ring optionally further having substituent(s), and
B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring) or a salt thereof, or a prodrug thereof;

[19] use of a compound represented by the formula (I):



(I)

wherein

Ar is a phenyl group optionally having substituent(s),
R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),
Z is a methylene group optionally having C_{1-6} alkyl

group(s), ring A is a piperidine ring optionally further having substituent(s), and B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring) or a salt thereof, or a prodrug thereof for the production of an agent for the prophylaxis or treatment of lower urinary tract disease, gastrointestinal disease or central nervous system disease; and the like.

Detailed Description of the Invention

Ar is a phenyl group optionally having substituent(s).

The substituent for the "phenyl group" includes, for example, 1 to 3 substituents selected from the group consisting of (1) halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), (2) C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{2-6} alkenyl, (7) optionally halogenated C_{2-6} alkynyl, (8) optionally halogenated C_{3-6} cycloalkyl, (9) C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl, etc.) optionally substituted with substituent(s) selected from the group consisting of cyano and halogen atom, (10) optionally halogenated C_{1-6} alkoxy, (11) optionally halogenated C_{1-6} alkylthio or mercapto, (12) hydroxy, (13) amino, (14) mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, etc.), (15) mono-C_{6-14} arylamino (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.), (16) di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, etc.), (17) di-C_{6-14} arylamino (e.g., diphenylamino, etc.), (18) acyl, (19) acylamino, (20) acyloxy, (21) 5- to 7-membered cyclic amino optionally having substituent(s),

(22) 5- to 10-membered aromatic heterocyclic group optionally substituted with optionally halogenated C_{1-6} alkyl (e.g., 1-, 2- or 3- pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5- pyrazolyl, 1- or 3-triazolyl, 1-, 2- or 5- tetrazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5- isothiazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5- isoxazolyl, furazanyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-pyrazinyl, 2-, 4- or 5-pyrimidinyl, 3- or 4-pyridazinyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, etc.), (23) sulfo, (24) C_{6-14} aryloxy (e.g., phenyloxy, naphthyloxy, etc.), (25) a group obtained by combining 1 to 3 group(s) of the above-mentioned (1)-(24) and the like.

The "optionally halogenated C_{1-6} alkyl" includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), optionally having 1 to 5, preferably 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine, etc.) and the like, specifically, methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.

The "optionally halogenated C_{2-6} alkenyl" includes, for example, C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, etc.) optionally having 1 to 5, preferably 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine, etc.) and the like, specifically, vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, 3,3,3-

trifluoro-1-propenyl, 4,4,4-trifluoro-1-butenyl, etc.

The "optionally halogenated C_{2-6} alkynyl" includes, for example, C_{2-6} alkynyl (e.g., ethynyl, propargyl, butynyl, 1-hexynyl, etc.) optionally having 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.) and the like, specifically, ethynyl, propargyl, butynyl, 1-hexynyl, 3,3,3-trifluoro-1-propynyl, 4,4,4-trifluoro-1-butynyl, etc.

The "optionally halogenated C_{3-6} cycloalkyl" includes, for example, C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) optionally having 1 to 5, preferably 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine, etc.) and the like, specifically, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl, etc.

The "optionally halogenated C_{1-6} alkoxy" includes, for example, C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.) optionally having 1 to 5, preferably 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine, etc.) and the like, specifically, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.

The "optionally halogenated C_{1-6} alkylthio" includes, for example, C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.) optionally having 1 to 5, preferably 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine, etc.) and the like, specifically, methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio, etc.

The "acyl" includes, for example, $-(C=O)-R^3$, $-(C=S)-R^3$, $-SO_2-R^3$, $-SO-R^3$, $-(P=O)(OR^4)(OR^{4\prime})$ (R^3 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an amino group optionally having substituent(s), a hydroxy group optionally having a substituent or a heterocyclic group optionally having substituent(s), and R^4 and $R^{4\prime}$ are the same or different and represents a hydrogen atom or a hydrocarbon group optionally having substituent(s)) and the like.

The "hydrocarbon group optionally having substituent(s)" represented by R^3, R^4 or $R^{4\prime}$ includes, for example, the same group as those referred to herein for the "hydrocarbon group optionally having substituent(s)" represented by R^1 which will be described below.

The "substituent" for the "amino group optionally having substituent(s)" represented by R^3 includes, for example, a hydrocarbon group optionally having substituent(s), a heterocyclic group optionally having substituent(s), a hydroxy group optionally having a substituent, an acyl group and the like.

The "hydrocarbon group optionally having substituent(s)" as the "substituent" for the "amino group optionally having substituent(s)" represented by R^3 includes, for example, the same group as those referred to herein for the "hydrocarbon group optionally having substituent(s)" represented by R^1 which will be described below.

The "heterocyclic group optionally having substituent(s)" as the "substituent" in the "amino group optionally having substituent(s)" represented by R^3 includes, for example, the same group as those referred to herein for the "heterocyclic group optionally having substituent(s)" represented by R^1 which will be described below.

The "hydroxy group optionally having a substituent" as the "substituent" for the "amino group optionally having substituent(s)" represented by R^3 includes, for example, (i) hydroxy group, (ii) C_{1-6} alkoxy group (e.g., methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, t-butoxy group, etc.), (iii) C_{6-14} aryloxy group (e.g., phenyloxy group, naphthyloxy group, etc.), (iv) formyloxy group or C_{1-6} alkyl-carbonyloxy group (e.g., acetoxy group, propionyloxy group, etc.) and (v) C_{6-14} aryl-carbonyloxy group (e.g., benzoyloxy group, naphthyl-carbonyloxy group, etc.) and the like, and preferably, hydroxy group and C_{1-6} alkoxy group (e.g., methoxy group, ethoxy group, propoxy group, isopropoxy group, etc.).

The "acyl group" as the "substituent" for the "amino group optionally having substituent(s)" represented by R^3 includes, for example, -(C=O)-R", -(C=S)-R", $-SO_2$-R", -SO-R", -(C=O)NR"R'", -(C=O)O-R", -(C=S)O-R", -(C=S)NR"R'" (R" is a hydrogen atom or a hydrocarbon group optionally having substituent(s), R"' is a hydrogen atom or a lower alkyl group (e.g., C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc., and particularly preferably C_{1-3} alkyl group such as methyl, ethyl, propyl, isopropyl, etc.)) and the like.

The "hydrocarbon group optionally having substituent(s)" represented by R" includes, for example, the same group as those referred to herein for the "hydrocarbon group optionally having substituent(s)" represented by R^1 which will be described below.

The "C_{1-6} alkoxy group", the "C_{6-14} aryloxy group", the "formyloxy group", the "C_{1-6} alkyl-carbonyloxy group" and the "C_{6-14} aryl-carbonyloxy group" exemplified as the "hydroxy group optionally having a substituent" as the "substituent" for the "amino group optionally having substituent(s)" represented by R^3, may be optionally further substituted with the same group(s) as those referred to herein for the "substituent" for the "hydrocarbon group optionally having substituent(s)" represented by R^1 which will be described below and the like, and such a substituent preferably includes a halogen atom (e.g., fluorine, chlorine, bromine, etc.) and the like.

The "amino group optionally having substituent(s)" represented by R^3 may form a cyclic amino group (e.g., 5- to 9-membered cyclic amino group optionally having 1 to 3 hetero atoms such as an oxygen atom, a sulfur atom, etc. in addition to a nitrogen atom (e.g., pyrrolidino group, piperidino group, piperazino group, morpholino group, etc.) and the like.

The "hydroxy group optionally having a substituent" represented by R^3 includes, for example, the same group as those referred to herein for the "hydroxy group optionally having a substituent" as the "substituent" for the above-mentioned "amino group optionally having substituent(s)" represented by R^3, and the like.

The "heterocyclic group optionally having substituent(s)" represented by R^3 includes, for example, the same group as those referred to herein for the "heterocyclic group optionally having substituent(s)" represented by R^1 which will be described below.

The "acylamino" as described above includes, for example, formylamino, C_{1-6} alkyl-carbonylamino (e.g., acetylamino, etc.), heterocycle-C_{1-6} alkyl-carbonylamino (e.g., piperidino-acetylamino optionally having oxo, etc.), C_{3-7} cycloalkyl-carbonylamino (e.g., cyclopropylcarbonylamino, etc.), C_{6-14} aryl-carbonylamino (e.g., phenylcarbonylamino, naphthylcarbonylamino, etc.), heterocycle-carbonylamino (e.g., thienylcarbonylamino, furylcarbonylamino, pyrrolylcarbonylamino, etc.), C_{1-6} alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, etc.), C_{6-14} aryloxy-carbonylamino (e.g., phenoxycarbonylamino, naphthoxycarbonylamino, etc.), heterocycleoxy-carbonylamino, C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), C_{6-14} arylsulfonylamino (e.g., phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino, etc.), heterocycle-sulfonylamino, ureido, mono- or di-C_{1-6} alkyl-ureido (e.g., methylureido, dimethylureido, etc.), mono- or di-C_{6-14} aryl-ureido (e.g., phenylureido, diphenylureido, etc.) and the like.

The "acyloxy" as described above includes, for example, formyloxy, C_{1-6} alkyl-carbonyloxy (e.g., acetoxy, propionyloxy, etc.), heterocycle-C_{1-6} alkyl-carbonyloxy, C_{3-7} cycloalkyl-carbonyloxy (e.g., cyclopropylcarbonyloxy, etc.), C_{6-14} aryl-carbonyloxy (e.g., benzoyloxy, naphthylcarbonyloxy, etc.), heterocycle-carbonyloxy (e.g., nicotinoyloxy), C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), C_{6-14} aryloxy-carbonyloxy, heterocycleoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-14} aryl-carbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), etc.

Here, as the heterocycle of heterocycle-C_{1-6}

alkyl-carbonylamino, heterocycle-carbonylamino, heterocycleoxy-carbonylamino, heterocycle-sulfonylamino, heterocycle-C_{1-6} alkyl-carbonyloxy, heterocycle-carbonyloxy and heterocycleoxy-carbonyloxy, for example, 5- to 14-membered (preferably 5- to 9-membered, more preferably 5- or 6-membered) non-aromatic heterocycle containing, besides carbon atoms, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (e.g., pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl and the like), or 5- to 14-membered (preferably 5- to 9-membered, more preferably 5- or 6-membered) aromatic heterocyclic group containing, besides carbon atoms, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl and the like), each of which optionally has one or two of halogen atom, optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, oxo and the like, and the like can be used.

The "5- to 7-membered saturated cyclic amino" for the "5- to 7-membered saturated cyclic amino optionally having substituent(s)" includes, for example, morpholino, thiomorpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, etc. The "substituent" in the "5- to 7-membered saturated cyclic amino optionally having substituent(s)" includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl, etc.), a 5- to 10-membered aromatic heterocyclic group (e.g., 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, etc.) and the like. The number of the substituents is 1 to 3.

As Ar, a phenyl group optionally having halogen atom (e.g., fluorine atom, etc.) or C_{1-6} alkyl (e.g., methyl, etc.) is preferable, and a phenyl group optionally substituted at the para-position and the like by fluorine atom or methyl is more preferable. Particularly preferred is an unsubstituted phenyl group.

R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s).

The "hydrocarbon group" for the "hydrocarbon group optionally having substituent(s)" represented by R^1 includes, for example, aliphatic hydrocarbon group, monocyclic saturated hydrocarbon group, aromatic hydrocarbon group, etc., preferably having 1 to 16 carbons, and specifically, for example, alkyl group, alkenyl group, alkynyl group, cycloalkyl group, aryl group, etc.

The "alkyl group" is preferably, for example, a lower alkyl group, etc., for example, C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "alkenyl group" is preferably, for example, a lower alkenyl group, etc., for example, C_{2-6} alkenyl group such as vinyl, 1-propenyl, allyl, isopropenyl, butenyl, isobutenyl, etc.

The "alkynyl group" is preferably, for example, lower alkynyl group, etc., for example, C_{2-6} alkynyl group such as ethynyl, propargyl, 1-propynyl, etc.

The "cycloalkyl group" is preferably, for example, lower cycloalkyl group, etc., for example, C_{3-6} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "aryl group" is preferably, for example, C_{6-14} aryl group such as phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl, etc., specifically, a phenyl group, etc.

The substituent that the "hydrocarbon group" for the "hydrocarbon group optionally having substituent(s)" represented by R^1 may have includes, for example, (1) halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom, etc.), (2) nitro group, (3) cyano group, (4) hydroxy group, (5) optionally halogenated lower alkyl group (e.g., optionally halogenated C_{1-6} alkyl group such as methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 4,4,4-trifluorobutyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.), (6) optionally halogenated C_{2-6} alkenyl, (7) optionally halogenated C_{2-6} alkynyl, (8) optionally halogenated C_{3-6} cycloalkyl, (9) optionally halogenated lower alkoxy group (e.g., C_{1-6} alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, etc.), (10) acyloxy group, (11) optionally halogenated C_{1-6} alkylthio group or mercapto group, (12) acyl group, (13) amino group, (14) mono-lower alkylamino group (e.g., mono-C_{1-6} alkylamino group such as methylamino, ethylamino, etc.), (15) di-lower alkylamino group (e.g., di-C_{1-6} alkylamino group such as dimethylamino, diethylamino, etc.), (16) mono-C_{6-14} arylamino (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.), (17) di-C_{6-14} arylamino group (e.g., diphenylamino, etc.), (18) acylamino group, (19) carboxyl group, (20) aryl group (e.g., C_{6-14} aryl group such as phenyl, naphthyl, biphenyl, 2-anthryl, etc.), (21) aryloxy group (e.g., C_{6-14} aryloxy group such as phenyloxy, naphthyloxy, etc.), (22) optionally halogenated lower alkylcarbonylamino group (e.g., optionally halogenated C_{1-6} alkyl-carbonylamino group such as acetylamino, trifluoroacetylamino, etc.), (23) optionally halogenated lower alkylsulfonyl group (e.g., optionally halogenated C_{1-6} alkylsulfonyl group such as methylsulfonyl, trifluoromethylsulfonyl, etc.), (24) optionally halogenated lower alkylsulfonylamino group (e.g., optionally halogenated C_{1-6} alkylsulfonylamino group such as methylsulfonylamino, trifluoromethylsulfonylamino, etc.), (25) optionally halogenated lower alkoxycarbonylamino group (e.g., optionally halogenated C_{1-6} alkoxy-carbonylamino group such as methoxycarbonylamino, trifluoromethoxycarbonylamino, etc.), (26) oxo group, (27) 5- to 7-membered cyclic amino optionally having substituent(s), (28) heterocyclic group, (29) C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), (30) carbamoyl group, (31) group obtained by combining 1 to 3 groups of the above-mentioned (1)-(30) and the like.

The "hydrocarbon group" for the "hydrocarbon group optionally having substituent(s)" optionally has 1 to 5, preferably 1 to 3 substituents mentioned above at the substitutable position(s) on the hydrocarbon group. When the number of the substituents is 2 or more, the substituents may be the same or different.

The "acyl" as the "substituent" for the "hydrocarbon group optionally having substituent(s)" represented by R^1 includes, for example, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.), heterocycle-C_{1-6} alkyl-carbonyl, C_{3-7} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, etc.), C_{6-14} aryl-carbonyl (e.g., phenylcarbonyl, naphthylcarbonyl, etc.), heterocycle-carbonyl (e.g., nicotinoyl, etc.), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), C_{6-14} aryloxy-carbonyl (e.g., phenoxycarbonyl, naphthoxycarbonyl, etc.), heterocycleoxy-carbonyl, C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.), C_{6-14} arylsulfonyl (e.g., phenylsulfonyl, 2-naphthylsulfonyl, 1-naphthylsulfonyl, etc.), heterocycle-sulfonyl, C_{1-6} alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.), C_{6-14} arylsulfinyl (e.g., phenylsulfinyl, naphthylsulfinyl, etc.), carbamoyl, thiocarbamoyl, mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, naphthylcarbamoyl, etc.) and the like. The heterocycle of the heterocycle-C_{1-6} alkyl-carbonyl, heterocycle-carbonyl, heterocycleoxy-carbonyl and heterocycle-sulfonyl includes, for example, 5- to 14-membered (preferably 5- to 9-membered, more preferably 5- or 6-membered) non-aromatic heterocycle containing, besides carbon atoms, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (e.g., pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, etc.) or 5- to 14-membered (preferably 5- to 9-membered, more preferably 5- or 6-membered) aromatic heterocyclic group containing, besides carbon atoms, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc.), each of which optionally has substituent(s) such as halogen atom, optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, oxo and the like, and the like.

The "acyloxy" and "acylamino" as the "substituent" for the "hydrocarbon group optionally having substituent(s)" represented by R^1 include the same group as those referred to herein for the aforementioned "acyloxy" and "acylamino" as the substituent of the "phenyl group optionally having substituent(s)" represented by Ar.

The "5- to 7-membered cyclic amino optionally having substituent(s)" as the "substituent" for the "hydrocarbon group optionally having substituent(s)" represented by R^1 includes the same group as those referred to herein for the aforementioned "5- to 7-membered cyclic amino optionally having substituent(s)" as the substituent of the "phenyl group optionally having substituent(s)" represented by Ar.

The "heterocyclic group" as the "substituent" for the "hydrocarbon group optionally having substituent(s)" represented by R^1 includes, for example, 5- to 14-membered (preferably 5- to 9-membered, more preferably 5- or 6-membered) aromatic heterocyclic group containing, besides carbon atoms, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc.) or 5- to 14-membered (preferably 5- to 9-membered, more preferably 5- or 6-membered) non-aromatic heterocyclic group containing, besides carbon atoms, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (e.g., pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, dihydrotriazolyl (e.g., 4,5-dihydro-1,2,4-triazol-3-yl, etc.), dihydropyrimidinyl (e.g., 3,4-dihydropyrimidin-1(2H)-yl, etc.), oxazolidinyl (e.g., oxazolidin-3-yl, etc.) and the like) and the like. These non-aromatic heterocyclic group is optionally further condensed with other aromatic or non-aromatic homocyclic ring or heterocycle. The "heterocyclic group" may also have substituent(s) such as halogen atom, optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, oxo and the like.

The "optionally halogenated lower alkyl group" as the "substituent" for the "hydrocarbon group optionally having substituent(s)" represented by R^1 includes the same group as those referred to herein for the aforementioned "optionally halogenated C_{1-6} alkyl group" as the substituent of the "phenyl group optionally having substituent(s)" represented by Ar.

The "optionally halogenated C_{2-6} alkenyl", "optionally halogenated C_{2-6} alkynyl", "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated a lower alkoxy group" and "optionally halogenated C_{1-6}

alkylthio group" as the "substituent" for the "hydrocarbon group optionally having substituent(s)" represented by R^1 include the same group as those exemplified herein as the aforementioned substituent of the "phenyl group optionally having substituent(s)" represented by Ar respectively.

The "acyl group" represented by R^1 includes, for example, the same group as those referred to herein above for the foregoing "acyl" as the substituent of the "phenyl group optionally having substituent(s)" represented by Ar.

The "heterocyclic group" for the "heterocyclic group optionally having substituent(s)" represented by R^1 includes, for example, 5- to 14-membered (preferably 5- to 10-membered) (monocyclic to tricyclic, preferably, monocyclic or dicyclic) aromatic or non-aromatic heterocyclic group containing 1 to 4 (preferably 1 to 3) hetero atoms of one or two kinds selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms, etc. For example, it includes 5-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom, such as 2- or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, etc., 6-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom, such as 2-, 3- or 4-pyridyl, 2-, 3- or 4-pyridyl N-oxide, 2-, 4- or 5-pyrimidinyl, 2-, 4- or 5-pyrimidinyl N-oxide, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, triazinyl, 3- or 4-pyridazinyl, pyrazinyl, 3- or 4-pyridazinyl N-oxide, etc., bicyclic or tricyclic fused cyclic group containing, besides carbon atoms, 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom, such as indolyl, benzofuryl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolyl, isoquinolyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolizinyl, quinolizinyl, 1,8-naphthyridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenanthridinyl, chromanyl, phenothiazinyl, phenoxazinyl, etc. (preferably, group formed by the fusion of the above-mentioned 5- or 6-membered ring to one or two of 5- or 6-membered cyclic groups optionally containing, besides carbon atoms, 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom), 5- or 6-membered non-aromatic heterocyclic group containing, besides carbon atoms, 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom, such as pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrazolidinyl, pyranyl, thiopyranyl, tetrahydrothiopyranyl, dihydropyrimidinyl (e.g., 3,4-dihydropyrimidin-6(2H)-yl), etc. Of these, 5- to 7-membered (preferably 5- or 6-membered) nitrogen-containing heterocyclic group containing 1 to 3 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom in addition to carbon atoms is preferred.

The substituent that the "heterocyclic group" for the "heterocyclic group optionally having substituent(s)" may have includes the same group as those referred to herein for the aforementioned substituent that the "hydrocarbon group" for the "hydrocarbon group optionally having substituent(s)" may have, for example, (1) halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), (2) lower alkyl group (e.g., C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), (3) cycloalkyl group (e.g., C_{3-6} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), (4) lower alkynyl group (e.g., C_{2-6} alkynyl group such as ethynyl, 1-propynyl, propargyl, etc.), (5) lower alkenyl group (e.g., C_{2-6} alkenyl group such as vinyl, allyl, isopropenyl, butenyl, isobutenyl, etc.), (6) aralkyl group (e.g., C_{7-11} aralkyl group such as benzyl, α-methylbenzyl, phenethyl, etc.), (7) aryl group (e.g., C_{6-10} aryl group such as phenyl, naphthyl, etc., preferably phenyl group, etc.), (8) lower alkoxy group (e.g., C_{1-6} alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.), (9) aryloxy group (e.g., C_{6-10} aryloxy group such as phenoxy, etc.), (10) acyl (e.g., formyl group, lower alkyl-carbonyl group (e.g., C_{1-6} alkyl-carbonyl group such as acetyl, propionyl, butyryl, isobutyryl, etc.) which is optionally substituted with the substituent(s) selected from the group consisting of hydroxy, formylamino, C_{1-6} alkyl-carbonylamino group (e.g., acetylamino, etc.) and 5- or 6-membered non-aromatic or aromatic heterocyclic group containing, besides carbon atoms, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (e.g., tetrazolyl, etc.), arylcarbonyl (e.g., C_{6-14} aryl-carbonyl group such as benzoyl group, naphthoyl group, etc.), carbamoyl group, sulfo group, sulfino group, phosphono group, sulfamoyl group, lower alkylsulfinyl group (e.g., C_{1-6} alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.), arylsulfinyl group (e.g., C_{6-14} arylsulfinyl group such as phenylsulfinyl, naphthylsulfinyl, etc.), lower alkylsulfonyl group (e.g., C_{1-6} alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, etc.), arylsulfonyl group (e.g., C_{6-14} arylsulfonyl group such as phenylsulfonyl, naphthylsulfonyl, etc.), monoalkylsulfamoyl group (e.g., mono-C_{1-6} alkylsulfamoyl group such as N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl, etc.), dialkylsulfamoyl group (e.g., di-C_{1-6} alkylsulfamoyl group such as N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.), etc.), (11) carboxyl group, (12) acyloxy group (e.g., formyloxy, lower alkyl-carbonyloxy group (e.g., C_{1-6} alkyl-carbonyloxy group such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.), arylcarbonyloxy group (e.g., C_{6-14} aryl-carbonyloxy group such as benzoyloxy, naphthoyloxy, etc.), lower alkoxycarbonyloxy group (e.g., C_{1-6} alkoxy-carbonyloxy group such as methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, tert-butoxycarbonyloxy, etc.), aralkyloxycarbonyloxy (e.g., C_{7-15} aralkyloxycarbonyloxy group such as benzyloxycarbonyloxy, etc.), (13) mono-, di- or tri-halogeno-lower alkyl group (e.g., mono-, di- or tri-halogeno-C_{1-6} alkyl group such as chloromethyl, dichloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, etc.), (14) oxo group, (15) amidino group, (16) imino group, (17) amino group, (18) mono-lower alkylamino group (e.g., mono-C_{1-6} alkylamino group such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), (19) di-lower alkylamino group (e.g., di-C_{1-4} alkylamino group such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, methylethylamino, etc.), (20) acylamino, (21) 3- to 6-membered cyclic amino group optionally containing, besides carbon atoms and one nitrogen atom, 1 to 3 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom (e.g., 3- to 6-membered cyclic amino group such as aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidinyl, morpholinyl, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc.), (22) alkylenedioxy group (e.g., C_{1-3} alkylenedioxy group such as methylenedioxy, ethylenedioxy, etc.), (23) hydroxy group, (24) nitro group, (25) cyano group, (26) mercapto group, (27) alkylthio group (e.g., C_{1-6} alkylthio group such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.), (28) arylthio group (e.g., C_{6-14} arylthio group such as phenylthio, naphthylthio, etc.), (29) a group obtained by combining 1 to 3 group(s) of the above-mentioned (1)-(28) and the like. Here, the "acyl", "acyloxy" and "acylamino" include the same group as those referred to herein for the above-mentioned "acyl", "acyloxy" and "acylamino", which are substituents that the "hydrocarbon group" in the "hydrocarbon group optionally having substituent(s)" may have.

The "heterocyclic group" for the "heterocyclic group optionally having substituent(s)" may have 1 to 5, preferably 1 to 3 of the above-mentioned substituents at the substitutable position(s) of the heterocyclic group. When the number of the substituents is 2 or more, the substituents may be the same or different.

R^1 is preferably a hydrogen atom or an acyl group. The acyl group is preferably a group represented by the following -(C=O)-R^5 (R^5 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an amino group optionally having substituent(s), a hydroxy group optionally having a substituent or a heterocyclic group optionally having substituent(s)).

The "hydrocarbon group optionally having substituent(s)", "amino group optionally having substituent(s)", "hydroxy group optionally having a substituent" or "heterocyclic group optionally having substituent(s)" represented by R^5 includes the same group as those referred to herein for the aforementioned "hydrocarbon group optionally having substituent(s)", "amino group optionally having substituent(s)", "hydroxy group optionally having a substituent" or "heterocyclic group optionally having substituent(s)" represented by R^3.

As the "hydrocarbon group optionally having substituent(s)" for R^5,

(1) C_{1-6} alkyl group (e.g., methyl group, ethyl group, etc.) optionally having 1 to 3 substituents selected from the group consisting of (i) formylamino, (ii) C_{1-6} alkyl-carbonylamino (e.g., acetylamino, etc.), (iii) C_{1-6} alkoxy-carbonylamino (e.g., methoxycarbonylamino, etc.), (iv) heterocyclic group optionally having substituent(s) selected from the group consisting of C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, etc.), hydroxy, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, etc.), formylamino, oxo and C_{1-6} alkyl-carbonylamino (e.g., acetylamino, etc.) (e.g., 5- or 6-membered aromatic or nonaromatic heterocyclic group containing, besides carbon atom, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom (e.g., 1,4-piperazinyl, piperazino, 1-piperidinyl, 4-piperidinyl, 1-pyrrolidinyl, imidazolyl, tetrazolyl, triazolyl,

dihydrotriazolyl, tetrahydropyrimidinyl, oxazolidinyl, etc.)), (v) carbamoyl group, (vi) hydroxy group and (vii) C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl, etc.) and the like,

(2) C_{3-7} cycloalkyl group (e.g., cyclohexyl group, etc.) optionally having 1 to 3 substituents selected from the group consisting of (i) formylamino, (ii) C_{1-6} alkyl-carbonylamino (e.g., acetylamino, etc.), (iii) C_{1-6} alkoxy-carbonylamino (e.g., methoxycarbonylamino, etc.) and (iv) heterocyclic group optionally having substituent(s) selected from the group consisting of C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, etc.), hydroxy, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, etc.), formylamino, oxo and C_{1-6} alkyl-carbonylamino (e.g., acetylamino, etc.) (e.g., 5- or 6-membered aromatic or nonaromatic heterocyclic group containing, besides carbon atom, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom (e.g., 1,4-piperazinyl, piperazino, 1-piperidinyl, 4-piperidinyl, imidazolyl, tetrazolyl, triazolyl, etc.)) and (v) carbamoyl group, and the like,

(3) C_{6-14} aryl group (e.g., phenyl group, etc.) optionally having 1 to 3 substituents selected from the group consisting of (i) formylamino group and (ii) C_{1-6} alkyl-carbonylamino group (e.g., acetylamino, etc.) and the like, and the like are preferable.

As the "amino group optionally having substituent(s)" for R^5, mono-C_{1-6} alkylamino group is preferable.

As the "hydroxy group optionally having a substituent" for R^5, C_{1-6} alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, etc.) is preferable.

As the "heterocyclic group optionally having substituent(s)" for R^5, 5- or 6-membered aromatic or nonaromatic heterocyclic group containing, besides carbon atom, 1 or 2 nitrogen atoms (particularly, 1-piperidinyl group, 4-piperidinyl group, 1,4-piperazinyl group, 5-imidazolyl group, 3-pyridyl group, 1,2,3,6-tetrahydropyrimidin-4-yl group), which optionally has 1 to 3 substituents selected from the group consisting of (i) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, etc.), (ii) C_{1-6} alkyl group having substituent(s) selected from the group consisting of formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, etc.), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, isopropoxycarbonyl, etc.), carbamoyl and mono- or di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, etc.), (iii) formyl group, (iv) C_{1-6} alkyl-carbonyl group optionally substituted by substituent(s) selected from the group consisting of hydroxy, formylamino, C_{1-6} alkyl-carbonylamino (e.g., acetylamino, etc.) and 5- or 6-membered nonaromatic or aromatic heterocyclic group containing, besides carbon atom, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom (e.g., tetrazolyl, etc.) (e.g., acetyl, hydroxyacetyl, etc.), (v) C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl, etc.) optionally substituted by substituent(s) selected from the group consisting of formylamino, C_{1-6} alkyl-carbonylamino (e.g., acetylamino, etc.) and 5- or 6-membered nonaromatic or aromatic heterocyclic group containing, besides carbon atom, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom (e.g., tetrazolyl, etc.), (vi) C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, t-butoxycarbonyl, etc.) optionally substituted by substituent(s) selected from the group consisting of formylamino, C_{1-6} alkyl-carbonylamino (e.g., acetylamino, etc.) and 5- or 6-membered nonaromatic or aromatic heterocyclic group containing, besides carbon atom, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom (e.g., tetrazolyl, etc.), (vii) substituent bonded via carbon atom such as heterocycle-carbonyl group optionally having 1 or 2 oxo (e.g., 5- or 6-membered aromatic or non-aromatic heterocycle containing, besides carbon atom, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom (e.g., imidazoline-carbonyl group, etc.) and the like, (viii) heterocyclic group optionally substituted by oxo (e.g., 5- or 6-membered aromatic or non-aromatic heterocycle containing, besides carbon atom, 1 to 4 of one or two kinds of hetero atoms selected from the group consisting of nitrogen atom, oxygen atom and sulfur atom (e.g., dihydrofuran-2(3H)-one, etc.) and (ix) oxo group and the like is preferable.

Particularly, as R^1, (1) a hydrogen atom, (2) a C_{1-6} alkyl-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl-carbonylamino group, (b) a 5- or 6-membered nitrogen-containing heterocyclic group optionally having 1 to 4 substituents selected from the group consisting of a C_{1-6} alkyl group and an oxo group, (c) a carbamoyl group, (d) a hydroxy group and (e) a C_{1-6} alkylsulfonyl group, (3) a C_{1-6} alkoxy-carbonyl group, (4) a C_{3-6} cycloalkyl-carbonyl group optionally having carbamoyl group(s), (5) a 5- or 6-membered nitrogen-containing heterocycle-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) an oxo group and (c) a C_{1-6} alkyl-carbonyl group optionally having hydroxy group(s), or (6) a monoC_{1-6} alkyl-carbamoyl group is preferable.

Z is a methylene group optionally having C_{1-6} alkyl group(s) such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, pentyl, hexyl and the like.

Z is preferably a methylene group.

Ring A is a piperidine ring optionally further having substituent(s). That is, ring A further optionally has 1 to 8 substituents besides R^1, -NH-Z-B and Ar.

The "substituent" of the "piperidine ring optionally having substituent(s)" includes those referred to herein for the aforementioned substituent of the "phenyl group optionally having substituent(s)" for Ar.

Ring A is preferably a piperidine ring having no substituent other than R^1, -NH-Z-B and Ar.

B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring).

As the "monocyclic aromatic heterocyclic group" of the "monocyclic aromatic heterocyclic group optionally having substituent(s)", a 5- or 6-membered monocyclic aromatic heterocyclic group containing, besides carbon atom, 1 to 4 hetero atom selected from the group consisting of nitrogen atom, oxygen atom, sulfur atom and the like (e.g., pyrrolyl group (1-, 2- or 3-pyrrolyl group), imidazolyl group (1-, 2-, 4- or 5-imidazolyl group), pyrazolyl group (1-, 3-, 4- or 5-pyrazolyl group), triazolyl group (1- or 3-triazolyl group), tetrazolyl group (1-, 2- or 5-tetrazolyl group), thiazolyl group (2-, 4- or 5-thiazolyl group), isothiazolyl group (3-, 4- or 5-isothiazolyl group), oxazolyl group (2-, 4- or 5-oxazolyl group), isoxazolyl group (3-, 4- or 5-isoxazolyl group), furazanyl group, furyl group (2- or 3-furyl group), thienyl group (2- or 3-thienyl group), pyridyl group (2-, 3- or 4-pyridyl group), pyrazinyl group, pyrimidinyl group (2-, 4- or 5-pyrimidinyl group), pyridazinyl group (3- or 4-pyridazinyl group), etc.) and the like can be mentioned.

As the "substituent" of the "monocyclic aromatic heterocyclic group optionally having substituent(s)", those referred to herein for the "substituent" of the "phenyl group optionally having substituent(s)" for Ar can be mentioned in the same number.

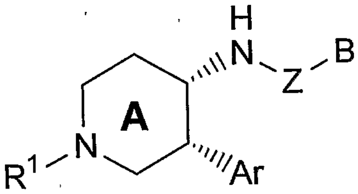
When the substituents of the "monocyclic aromatic heterocyclic group optionally having substituent(s)" for B are bonded to each other to form a ring, the monocyclic aromatic heterocyclic group is condensed with a ring (e.g., C_{3-8} cycloalkane ring (e.g., cyclopropane ring, cyclobutane ring, cyclopentane ring, cyclohexane ring, cycloheptane ring, cyclooctane ring, etc.), C_{6-10} aryl ring (e.g., benzene ring, naphthalene ring, etc.), heterocycle (e.g., pyrrole ring, imidazole ring, pyrazole ring, triazole ring, tetrazole ring, thiazole ring, isothiazole ring, oxazole ring, isoxazole ring, furazan ring, furan ring, thiophene ring, pyridine ring, pyrazine ring, pyrimidine ring, pyridazine ring, etc.), etc.).

As B, a nitrogen-containing aromatic heterocyclic group optionally having substituent(s) (e.g., pyrrolyl group (1-, 2- or 3-pyrrolyl group), imidazolyl group (1-, 2-, 4- or 5-imidazolyl group), pyrazolyl group (1-, 3-, 4- or 5-pyrazolyl group), triazolyl group (1- or 3-triazolyl group), tetrazolyl group (1-, 2- or 5-tetrazolyl group), thiazolyl group (2-, 4- or 5-thiazolyl group), isothiazolyl group (3-, 4- or 5-isothiazolyl group), oxazolyl group (2-, 4- or 5-

oxazolyl group), isoxazolyl group (3-, 4- or 5-isoxazolyl group), furazanyl group, pyridyl group (2-, 3- or 4-pyridyl group), pyrazinyl group, pyrimidinyl group (2-, 4- or 5-pyrimidinyl group), pyridazinyl group (3- or 4-pyridazinyl group), etc.) and the like are preferable.

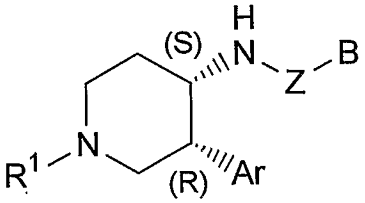
As B, (1) a pyridyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-6} alkyl group, (c) a hydroxy group, (d) a C_{1-6} alkoxy group, (e) a C_{6-10} aryl group optionally having cyano group(s) and (f) a nitrogen-containing aromatic heterocyclic group optionally substituted by C_{1-6} alkyl group(s) optionally having halogen atom(s), (2) a pyrimidyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) a C_{1-6} alkoxy group optionally having halogen atom(s) and (c) a C_{3-6} cycloalkyl group, (3) a pyrazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group optionally having halogen atom(s) or (4) a thiazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group are particularly preferable.

As compound (I), an optically active form represented by the formula (I-a)



(I-a)

wherein each symbol is as defined above, is preferable, and particularly, an optically active form represented by the formula (I-b)



(I-b)

wherein each symbol is as defined above, is preferable.

More specifically, an optically active form (I-b) wherein Ar is a phenyl group,

R^1 is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl-carbonylamino group, (b) a 5- or 6-membered nitrogen-containing heterocyclic group optionally having 1 to 4 substituents selected from the group consisting of a C_{1-6} alkyl group and an oxo group, (c) a carbamoyl group, (d) a hydroxy group and (e) a C_{1-6} alkylsulfonyl group,

(3) a C_{1-6} alkoxy-carbonyl group,

(4) a C_{3-6} cycloalkyl-carbonyl group optionally having carbamoyl group(s),

(5) a 5- or 6-membered nitrogen-containing heterocycle-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) an oxo group and (c) a C_{1-6} alkyl-carbonyl group optionally having hydroxy group(s), or

(6) a mono-C_{1-6} alkyl-carbamoyl group,

Z is a methylene group, and

B is (1) a pyridyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-6} alkyl group, (c) a hydroxy group, (d) a C_{1-6} alkoxy group, (e) a C_{6-10} aryl group optionally having cyano group(s) and (f) a nitrogen-containing aromatic heterocyclic group optionally substituted by C_{1-6} alkyl group(s) optionally having halogen atom(s),

(2) a pyrimidyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) a C_{1-6} alkoxy group optionally having halogen atom(s) and (c) a C_{3-6} cycloalkyl group, (3) a pyrazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group optionally having halogen atom(s) or (4) a thiazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group is preferable.

More specifically, N-{2-[(3R,4S)-4-({[5-(4-cyanophenyl)-2-methoxypyridin-3-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide (Example 1), N-(2-{(3R,4S)-4-[({2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]pyridin-3-yl}methyl)amino]-3-phenylpiperidin-1-yl}-2-oxoethyl)acetamide (Example 7), N-[2-((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide (Example 9), N-{2-[(3R,4S)-4-({[1-(4-bromophenyl)-3-methoxy-1H-pyrazol-4-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide (Example 23) and the like are preferable.

The salt of compound (I) includes, for example, a metal salt, an ammonium salt, a salt with an organic base, a salt with an inorganic acid, a salt with an organic acid, a salt with basic or acidic amino acid, etc. Suitable examples of the metal salt include an alkali metal salt such as a sodium salt, a potassium salt, etc.; an alkaline earth metal salt such as a calcium salt, a magnesium salt, a barium salt, etc.; an aluminum salt, etc. Suitable examples of the salts with an organic base include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. Suitable examples of the salts with an inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. Suitable examples of the salts with an organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. Suitable examples of the salts with a basic amino acid include salts with arginine, lysine, ornithine, etc. Suitable examples of the salts with an acidic amino acid include salts with asparaginic acid and glutamic acid, etc.

Of these, pharmaceutically acceptable salts are preferred. For example, if the compound has an acidic functional group, preferred are inorganic salts such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, barium salt, etc.), an ammonium salt, etc. If the compound has a basic functional group, preferred are salts with an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc., or salts with an organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluene sulfonic acid, etc.

The prodrug of the compound (I) or a salt thereof of the present invention means a compound which is converted to the compound (I) of the present invention under the physiological condition in the living body by a reaction with an enzyme, a gastric acid, or the like, that is, by enzymatic oxidation, reduction, hydrolysis, etc. or by hydrolysis with gastric acid, etc.

The prodrug of the compound (I) of the present invention includes a compound wherein the amino group of the compound (I) of the present invention is modified with acyl, alkyl or phosphoryl (e.g., a compound wherein the amino group of the compound (I) of the present invention is modified to eicosanoyl, alanyl, pentylaminocarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, tert-butyl, etc.); a compound wherein the hydroxy group of the compound (I) of the present invention is modified with acyl, alkyl, phosphoryl or boryl (e.g., a compound wherein the hydroxy group of the compound (I) of the present invention is modified with acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl or dimethylaminomethylcarbonyl, etc.); a compound wherein a carboxyl group of the compound (I) of the present invention is modified to ester or amide (e.g., a compound wherein a carboxyl group of the compound (I) of the present invention is modified to ethyl ester, phenyl ester, carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, cyclohexyloxycarbonylethyl ester or methylamide, etc.); etc. These compounds can be prepared by a method known *per se* from the compound (I) of the present invention.

In addition, the prodrug of the compound (I) of the present invention may be a compound, which is converted into the compound (I) of the present invention under the physiological conditions, as described in "Pharmaceutical Research and Development", Vol. 7 (Drug Design), pp. 163-198 (1990), published by Hirokawa Publishing Co.

Solvate, for example, hydrates of the compound represented by the formula (I) and a salt thereof are all included in the scope of the present invention. The compound represented by the formula (I) may be labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I, etc.) and the like.

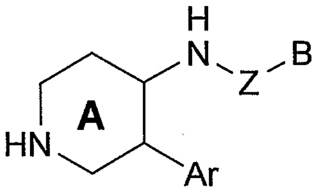
If the compound (I) of the present invention according to the present invention has chiral center, isomers such as an enantiomer or a diastereomer may exist. Such isomers and a mixture thereof are all included in the scope of the present invention. In addition, there can be instances where the conformational isomers are generated in cases, but such isomers or a mixture thereof are also included in compound (I) or a salt thereof of the present invention. Compound (I) is preferably a cis-isomer in view of activity.

A method of preparing compound (I) or a salt thereof of the present invention will be explained in the following.

Compound (I) or a salt thereof of the present invention can be prepared according to a method described in WO 03/101964, specifically, using Method A or Method B below.

[Method A]

Compound (I) or a salt thereof of the present invention can be prepared by subjecting a compound represented by the formula (Ib):



(Ib)

wherein each symbol is as defined above or a salt thereof (hereinafter to be referred to as compound (Ib)), to a reaction with a compound represented by the formula (III):

R^{1a}-OH (III)

wherein R^{1a} is a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s), which is an acylating agent or an alkylating agent, a salt thereof or a reactive derivative thereof.

The "hydrocarbon group optionally having substituent(s), the acyl group or the heterocyclic group optionally having substituent(s)" represented by R^{1a} includes the same group as those referred to herein above for the foregoing group represented by R^1.

The reactive derivative of the compound (III) includes, for example, a compound represented by the formula (IIIa):

R^{1a}-L (IIIa)

wherein L is a leaving group, and R^{1a} is as defined above, or a salt thereof (hereinafter to be referred to as a reactive derivative (IIIa)).

The leaving group represented by L includes, for example, halogen atom (e.g., chlorine atom, bromine atom, iodine atom, etc.), substituted sulfonyloxy group (e.g., C_{1-6} alkylsulfonyloxy group such as methanesulfonyloxy, ethanesulfonyloxy, etc.; C_{6-14} arylsulfonyloxy group such as benzenesulfonyloxy, p-toluenesulfonyloxy, etc.; and C_{7-16} aralkylsulfonyloxy group such as benzylsulfonyloxy group, etc.), acyloxy (acetoxy, benzoyloxy, etc.), carbonates, trichloroacetoimidates, oxalates, phosphites (e.g., methyl phosphite, etc.), phosphoranes, oxy group substituted with hetero ring or aryl group (succinimide, benzotriazole, quinoline, 4-nitrophenyl, etc.), hetero ring (imidazole, etc.) and the like.

The reaction using the above-mentioned reactive derivative as an alkylating agent can be carried out by subjecting the compound (Ib) to a reaction with the reactive derivative, usually in a solvent in the presence of base. The solvent includes, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as dimethoxyethane, dioxane, tetrahydrofuran, etc., ketones such as acetone, etc., nitriles such as acetonitrile, etc., amides such as N,N-dimethylformamide, etc., sulfoxides such as dimethyl sulfoxide, etc., water and the like, which may be used in a suitable mixture. The base includes, for example, an organic base such as trimethylamine, triethylamine, N-methylmorpholine, pyridine, picoline, N,N-dimethylaniline, etc., and an inorganic base such as potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, etc. The amount of the base to be used is, for example, about 1 to about 100 molar equivalents, preferably about 1 to about 10 molar equivalents, per 1 mole of the compound (Ib).

The reactive derivative includes, for example, halides (e.g., chloride, bromide, iodide, etc.), sulfuric acid esters, or sulfonic acid esters (e.g., methanesulfonate, p-toluenesulfonate, benzenesulfonate, etc.) and the like, and particularly halides. The amount of the reactive derivative to be used is, for example, 1 to 5 molar equivalents, preferably 1 to 3 molar equivalents, per 1 mole of the compound (Ib).

Where necessary, the reaction can be promoted by adding an additive. Such an additive includes, for example, iodides such as sodium iodide, potassium iodide, etc. and the amount to be used is about 0.1 to 10 molar equivalents, preferably about 0.1 to 5 molar equivalents, per 1 mole of the substrate.

The reaction temperature is generally -10°C to 200°C, preferably about 0°C to 110°C, and the reaction time is generally 0.5 to 48 hrs, preferably 0.5 to 16 hrs.

The reaction using the above-mentioned reactive derivative as an acylating agent depends on the kind of reactive derivative or the compound (Ib), but it is usually carried out in a solvent. If necessary, a suitable base may be added to promote the reaction. The solvent includes, for example, hydrocarbons such as benzene, toluene, etc., ethers such as ethyl ether, dioxane, tetrahydrofuran, etc., halogenated hydrocarbons such as chloroform, dichloromethane, etc., esters such as ethyl acetate, etc., amides such as N,N-dimethylformamide, etc., aromatic amines such as pyridine, etc., water and the like, which may be used in a suitable mixture. In addition, the base includes, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, etc., hydrogen carbonates such as sodium hydrogen carbonate, potassium hydrogen carbonate, etc., carbonate such as sodium carbonate, potassium carbonate, etc., acetate such as sodium acetate, tertiary amines such as trimethylamine, triethylamine, N-methylmorpholine, etc., aromatic amines such as pyridine, picoline, N,N-dimethylaniline, etc. and the like. The amount of the base to be used is, for example, about 1 to about 100 molar equivalents, preferably about 1 to about 10 molar equivalents, per 1 mole of the compound (Ib).

The acylating agent includes, for example, carboxylic acid, sulfonic acid, phosphoric acid, carbonic acid or a reactive derivative thereof (e.g., acid halide, acid anhydride, mixed acid anhydride, active ester, etc.), isocyanic acid ester, isothiocyanic acid ester and the like.

The amount of such an acylating agent to be used is usually 1 to 10 molar equivalents, preferably 1 to 3 molar equivalents, per 1 mole of the compound (Ib). The reaction temperature is generally -10°C to 150°C, preferably about 0°C to 100°C, and the reaction time is generally 15 min to 24 hrs, preferably 30 min to 16 hrs.

The compound (Ib) used as the starting material in Method A can be prepared by subjecting the compound (Ia) obtained by Method B mentioned below to deacylation.

Such deacylation can be carried out according a known method, for example, the method described in Theodora W. Greene, Peter G. M. Wuts, "Protective Groups in Organic Synthesis, 3rd Ed.," (1999) Wiley-Interscience, and the like, or an analogous method thereto. The reaction is usually carried out in the presence of an acid or a base, if necessary, in a solvent that does not adversely influence the reaction though it depends on the kinds of the compound (Ia).

The acid is preferably mineral acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, etc.), carboxylic acids (e.g., acetic acid, trifluoroacetic acid, trichloroacetic acid, etc.), sulfonic acids (e.g., methanesulfonic acid, toluenesulfonic acid, etc.), Lewis acids (e.g., aluminum chloride, tin chloride, zinc bromide, etc.) and the like. If necessary, it may be used in a mixture of two or more. The amount of the acid to be used varies depending on the kinds of the solvent and other reaction conditions, but it is usually about 0.1 molar equivalents or more, per 1 mole of the compound (Ia), and the acid can be used as a solvent.

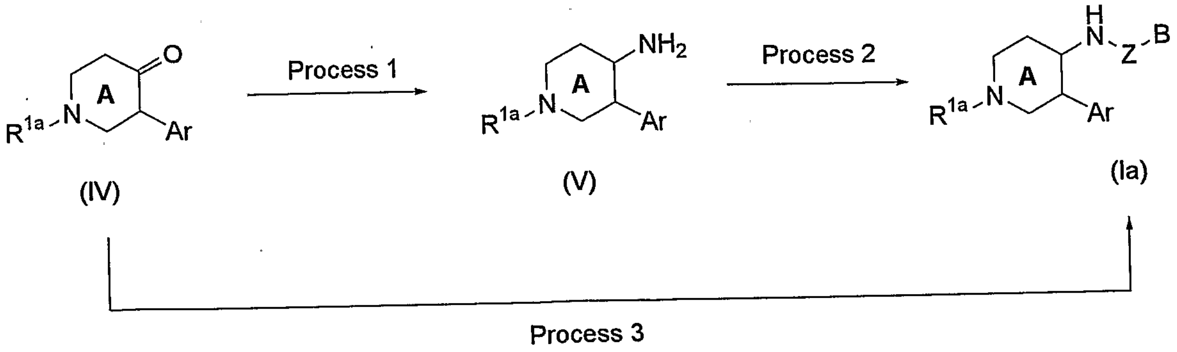
The base is preferably an inorganic base (alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, etc., alkali metal hydrogen carbonates such as sodium hydrogen carbonate, potassium hydrogen carbonate, etc., alkali metal carbonates such as sodium carbonate, potassium carbonate, etc., alkoxides such as sodium methoxide, sodium ethoxide, etc. and the like), or an organic base (amines such as trimethylamine, triethylamine, diisopropylethylamine, etc., cyclic amines such as pyridine, 4-dimethylaminopyridine, etc.) and the like, and particularly, sodium hydroxide, potassium hydroxide, sodium ethoxide and the like.

The amount of the base to be used varies depending on the kinds of the solvent and other reaction conditions, but is generally about 0.1 to about 10 molar equivalents, preferably about 0.1 to about 5 molar equivalents, per 1 mole of the compound (Ia).

The solvent that does not adversely influence the reaction includes, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, tert-butanol, etc.; aromatic hydrocarbons such as benzene, toluene, xylene, etc.; aliphatic hydrocarbons such as hexane, heptane, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, etc.; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, dimethoxyethane, etc.; nitriles such as acetonitrile, etc.; esters such as ethyl acetate, etc.; carboxylic acids such as acetic acid, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethyl sulfoxide, etc.; water and the like. Such a solvent may be used in a mixture of two or more at a suitable ratio.

The reaction temperature is for example, about -50°C to about 200°C, preferably about 0°C to about 100°C, and the reaction time varies depending on the kinds of the compound (Ia), the reaction temperature and the like, and it is for example, about 0.5 to about 100 hrs, preferably about 0.5 to about 24 hrs.

[Method B]



wherein each symbol is as defined above.

The compound (IV) used as the starting material in this Method can be prepared according to a method described in WO 03/101964.

(Process 1)

The present process is a process of converting a compound represented by the formula (IV) (hereinafter to be referred to as compound (IV)) to imine or oxime, followed by reducing it to thus prepare a compound represented by the formula (V) (hereinafter to be referred to as the amine compound (V)).

Conversion of the compound (IV) into the imine or oxime can be carried out by using a known method. For example, the reaction can be carried out by using various amines in a solvent inert to the reaction.

The amines include, for example, ammonia such as aqueous ammonia, ammonium chloride, ammonium acetate, etc., hydroxyamines such as hydroxyamine, O-methylhydroxyamine, O-benzylhydroxyamine, etc., organic amines such as benzylamine, aminodiphenylmethane, 1-phenylethylamine, etc., and may be used as a salt form such as hydrochloride, sulfate, etc. or as an aqueous solution thereof. The amount of the amine to be used is, for example, about 1 to 50 molar equivalents, preferably about 1 to 10 molar equivalents, per 1 mole of the compound (IV).

The solvent which is inert to the reaction includes, for example, aromatic hydrocarbons such as toluene, xylene, etc., aliphatic hydrocarbons such as heptane, hexane, etc., halogenated hydrocarbons such as chloroform, dichloromethane, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, etc., alcohols such as methanol, ethanol, 2-propanol, butanol, benzyl alcohol, etc., nitriles such as acetonitrile, etc., N,N-dimethylformamide, dimethyl sulfoxide, and the like. These solvents may be used in a mixture at a suitable ratio.

If necessary, the reaction can advantageously proceed by adding a catalyst. Such catalyst is preferably mineral acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, etc.), carboxylic acids (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, etc.), sulfonic acids (e.g., methanesulfonic acid, p-toluenesulfonic acid, etc.), Lewis acids (e.g., aluminum chloride, zinc chloride, zinc bromide, boron trifluoride, titanium chloride, etc.), acetate (e.g., sodium acetate, potassium acetate, etc.), molecular sieves (e.g., molecular sieves 3A, 4A, 5A, etc.), dehydrating agent (e.g., magnesium sulfate, etc) and the like. The amount of the catalyst to be used is, for example, about 0.01 to 50 molar equivalents, preferably about 0.1 to 10 molar equivalents, per 1 mole of the compound (IV).

The reaction temperature is generally about 0°C to 200°C, preferably about 20°C to 150°C, and the reaction time is generally 0.5 to 48 hrs, preferably 0.5 to 24 hrs.

The conversion of the imine or oxime into the amine compound (V) can be carried out according to various reduction reactions in a solvent inert to the reaction. The reduction reactions can be carried out by a method known *per se*, for example, a method using metal hydride or a method by catalytic hydrogenation.

The metal hydride includes, for example, sodium borohydride, lithium borohydride, zinc borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, lithium cyanoborohydride, diisobutylaluminum hydride, aluminum hydride, lithium aluminum hydride, a borane complex (a borane-THF complex, catechol borane, etc.) and the like, with preference given to sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, etc. The amount of the metal hydride to be used is, for example, about 1 to about 50 molar equivalents, preferably about 1 to about 10 molar equivalents, per 1 mole of the imine or oxime.

The reduction reaction using metal hydride is generally carried out in a solvent inert to the reaction. Such solvent includes, for example, aromatic hydrocarbons such as toluene, xylene, etc., aliphatic hydrocarbons such as heptane, hexane, etc., halogenated hydrocarbons such as chloroform, dichloromethane, etc., ethers such as diethyl ether, tetrahydrofuran, dioxane, etc., alcohols such as methanol, ethanol, 2-propanol, butanol, benzyl alcohol, etc., nitriles such as acetonitrile, etc., N,N-dimethylformamide, dimethyl sulfoxide and the like. These solvents may be used in a mixture at a suitable ratio.

The reaction temperature is generally about -80°C to 80°C, preferably about -40°C to 40°C, and the reaction time is generally 5 min to 48 hrs, preferably 1 to 24 hrs.

The catalytic hydrogenation can be carried out under a hydrogen atmosphere and in the presence of a catalyst. The catalyst is preferably palladium compounds such as palladium carbon, palladium hydroxide, palladium oxide, etc., nickel compounds such as nickel sponge catalyst, etc., platinum compounds such as platinum oxide, platinum carbon, etc., rhodium compounds such as rhodium carbon, etc. and the like, and the amount to be used is about 0.001 to about 1 molar equivalents, preferably about 0.01 to about 0.5 molar equivalents, per 1 mole of the imine or oxime.

The catalytic hydrogenation is generally carried out in a solvent inert to the reaction. Such solvent includes, for example, alcohols such as methanol, ethanol, propanol, butanol, etc.; hydrocarbons such as benzene, toluene, xylene, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, etc.; ethers such as diethyl ether, dioxane, tetrahydrofuran, etc.; esters such as ethyl acetate, etc.; amides such as N,N-dimethylformamide, etc.; carboxylic acids such as acetic acid, etc.; water, or a mixture thereof.

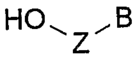
The hydrogen pressure under which the reaction is carried out, is generally about 1 to 50 atm, preferably about 1 to 10 atm. The reaction temperature is generally about 0°C to 150°C, preferably about 20°C to 100°C, and the reaction time is generally 5 min to 72 hrs, preferably 0.5 to 40 hrs.

In the present process, the amine compound (V) can be also prepared directly from the compound (IV) while carrying out the following reduction reaction without isolating imine or oxime which is an intermediate. In this case, pH of the reaction mixture is preferably from about 4 to about 5.

(Process 2)

In this step, the amine compound (V) is converted to the compound (Ia) by subjecting the amine compound (V) to an alkylation reaction or a reductive alkylation reaction.

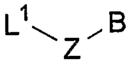
The alkylation reaction can be carried out by a method known *per se*. For example, the alkylation reaction can be carried out by subjecting the amine compound (V) to a reaction with a compound represented by the formula (VI):



(VI)

wherein each symbol is as defined above, or a salt thereof (hereinafter to be referred to as compound (VI)), which is an alkylating agent, or a reactive derivative thereof.

The reactive derivative of the compound (VI) includes, for example, a compound represented by the formula (VIa):



(VIa)

wherein L^1 is a leaving group, and each of the other symbols is as defined above, or a salt thereof (hereinafter to be referred to as a reactive derivative (VIa)).

The leaving group represented by L^1 includes, for example, halogen atom (e.g., chlorine atom, bromine atom, iodine atom, etc.), substituted sulfonyloxy group (e.g., C_{1-6} alkylsulfonyloxy group such as methanesulfonyloxy, ethanesulfonyloxy, etc.; C_{6-14} arylsulfonyloxy group such as benzenesulfonyloxy, p-toluenesulfonyloxy, etc.; and C_{7-16} aralkylsulfonyloxy group such as a benzylsulfonyloxy group, etc.; C_{1-6} alkoxysulfonyloxy group such as methoxysulfonyloxy, etc.) and the like.

The reaction using the compound (VI) or the above-mentioned reactive derivative (VIa) as an alkylating agent can be carried out by subjecting the amine compound (V) to a reaction with the compound (VI) or the reactive derivative (VIa), usually in a solvent in the presence of base though it depends on the kinds of the compound (VI), the reactive derivative (VIa) or the amine compound (V).

The solvent includes, for example, alcohols such as methanol, ethanol, propanol, etc., ethers such as dimethoxyethane, dioxane, tetrahydrofuran, etc., ketones such as acetone, etc., nitriles such as acetonitrile, etc., amides such as N,N-dimethylformamide, etc., sulfoxides such as dimethyl sulfoxide, etc., water and the like, which may be used in a suitable mixture.

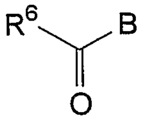
The base includes, for example, an organic base such as trimethylamine, triethylamine, N-methylmorpholine, pyridine, picoline, N,N-dimethylaniline, etc., and an inorganic base such as potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, etc. The amount of the base to be used is, for example, about 1 to about 100 molar equivalents, preferably about 1 to about 10 molar equivalents, per 1 mole of the amine compound (V).

The reactive derivative (VIa) includes, for example, halides (e.g., chloride, bromide, iodide, etc.), sulfuric acid esters, or sulfonic acid esters (e.g., methanesulfonate, p-toluenesulfonate, benzenesulfonate, etc.) and the like, and particularly halides. The amount of the compound (VI) or the reactive derivative (VIa) to be used is, for example, about 1 to about 5 molar equivalents, preferably about 1 to about 3 molar equivalents, per 1 mole of the amine compound (V).

If necessary, the reaction can be promoted by adding an additive. Such an additive includes, for example, iodides such as sodium iodide, potassium iodide, etc. and the amount to be used is about 0.1 to about 10 molar equivalents, preferably about 0.1 to about 5 molar equivalents, per 1 mole of the amine compound (V).

The reaction temperature is generally about -10°C to about 200°C, preferably about 0°C to about 110°C, and the reaction time is generally about 0.5 to about 48 hrs, preferably about 0.5 to about 16 hrs.

The reductive alkylation reaction can be carried out by a method known *per se*, for example, by reacting the amine compound (V) with a compound represented by the formula (VII):



(VII)

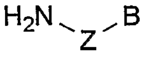
wherein R^6 is a hydrogen atom or C_{1-6} alkyl group, and each of the other symbol is as defined above, or a salt thereof (hereinafter to be referred to as compound (VII)), and reducing the prepared imine or iminium ion.

The reaction to prepare imine or iminium ion and to reduce the product can be carried out according to the method described in Process 1.

In the present process, the compound (Ia) can be also prepared directly from the amine compound (V) while carrying out the following reduction reaction without isolating imine or iminium ion which is an intermediate. In this case, pH of the reaction mixture is preferably from about 4 to about 5.

(Process 3)

The present process is a process for converting the compound (IV) into the compound (Ia) by reductive amination. The present reaction can be carried out by the known method *per se*, for example, by reacting the compound (IV) with a compound represented by the formula (VIII):



(VIII)

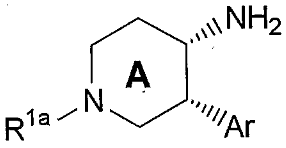
wherein each symbol is as defined above, or a salt thereof (hereinafter to be referred to as compound

(VIII)), and reducing the prepared imine or iminium ion.

The reaction to prepare imine or iminium ion and to reduce the product can be carried out according to the method described in Process 1.

In the present process, the compound (Ia) can be also prepared directly from the compound (IV) while carrying out the following reduction reaction without isolating imine or iminium ion which is an intermediate. In this case, pH of the reaction mixture is preferably from about 4 to about 5.

In the above-mentioned method, optically active compound (I) can be produced using, as a starting compound, an optically active compound represented by the formula (Va)



(Va)

wherein each symbol is as defined above, instead of compound (V). Compound (Va) to be used as a starting compound in this method can be produced according to the production method described in WO03/101964 and the like.

When compound (I) is obtained in a free form in the above-mentioned method, a salt with for example, inorganic acids (e.g., hydrochloric acid, sulfuric acid, hydrobromic acid, etc.), organic acids (e.g., methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, oxalic acid, fumaric acid, maleic acid, tartaric acid, etc.), inorganic bases (e.g., alkali metals such as sodium, potassium, etc., alkaline earth metals such as calcium, magnesium, etc., aluminum, ammonium, and the like), or organic bases (e.g., trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc.) and the like can be prepared in a routine manner. When compound (I) is obtained in the form of a salt, the compound can be converted to a free compound or another salt in a routine manner.

In addition, when the starting compound may form a salt in each of the above-mentioned reactions, the compound may be used as a salt. Such salt includes, for example, those exemplified as a salt of compound (I).

Compound (I) of the present invention thus prepared by such methods, can be isolated and purified by a typical separation means such as recrystallization, distillation, chromatography, etc.

When compound (I) contains an optical isomer, a stereoisomer, a regioisomer or a rotamer, these are also included in compound (I), and can be obtained as a single product according to synthesis and separation methods known *per se* (e.g., concentration, solvent extraction, column chromatography, recrystallization, etc.). For example, when compound (I) has an optical isomer, the optical isomer resolved from this compound is also included in compound (I).

The optical isomer can be prepared by a method known per se. To be specific, an optically active synthetic intermediate is used, or the final racemate product is subjected to optical resolution according to a conventional method to give an optical isomer.

The method of optical resolution may be a method known *per se*, such as a fractional recrystallization method, a chiral column method, a diastereomer method, etc.

1) Fractional recrystallization method

A method wherein a salt of a racemate with an optically active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.) is formed, which is separated by a fractional recrystallization method, and if desired, a free optical isomer is obtained by a neutralization step.

2) Chiral column method

A method wherein a racemate or a salt thereof is applied to a column for separation of an optical isomer (a chiral column) to allow separation. In the case of a liquid chromatography, for example, a mixture of the optical isomers is applied to a chiral column such as ENANTIO-OVM (manufactured by Tosoh Corporation), CHIRAL series (manufactured by Daicel Chemical Industries, Ltd.) and the like, and developed with water, various buffers (e.g., phosphate buffer) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.) solely or in admixture to separate the optical isomer. In the case of a gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (manufactured by GL Sciences Inc.) and the like is used to allow separation.

3) Diastereomer method

A method wherein a racemic mixture is prepared into a diastereomeric mixture by chemical reaction with an optically active reagent, which is made into a single substance by a typical separation means (e.g., a fractional recrystallization method, a chromatography method, etc.) and the like, and is subjected to a chemical treatment such as hydrolysis and the like to separate an optically active reagent moiety, whereby an optical isomer is obtained. For example, when compound (I) contains hydroxy, or primary or secondary amino group within a molecule, the compound and an optically active organic acid (e.g., MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid, etc.) and the like are subjected to condensation reaction to give diastereomers of the ester compound or the amide compound, respectively. When compound (I) has a carboxylic acid group, this compound and an optically active amine or an alcohol reagent are subjected to condensation reaction to give diastereomers of the ester compound or the amide compound, respectively. The separated diastereomer is converted to an optical isomer of the original compound by acid hydrolysis or base hydrolysis.

Compound (I) may be in the form of a crystal.

The crystal of compound (I) can be prepared by crystallization of compound (I) by a crystallization method known *per se*.

Examples of the crystallization method include a method of crystallization from a solution, a method of crystallization from vapor, a method of crystallization from the melts and the like.

The "crystallization from a solution" is typically a method of shifting a non-saturated state to supersaturated state by varying factors involved in solubility of compounds (solvent composition, pH, temperature, ionic strength, redox state, etc.) or the amount of solvent. To be specific, for example, a concentration method, a cold removing method, a reaction method (a diffusion method, an electrolysis method), a hydrothermal growth method, a flux method and the like can be mentioned. Examples of the solvent to be used include aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethyl sulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water and the like. These solvents are used alone or in a combination of two or more at a suitable ratio (e.g., 1:1 to 1:100 (a volume ratio)). Where necessary, a seed crystal can also be used.

The "crystallization from vapor" is, for example, a vaporization method (a sealed tube method, a gas stream method), a gas phase reaction method, a chemical transportation method and the like.

The "crystallization from the melts" is, for example, a normal freezing method (a Czockralski method, a temperature gradient method and a Bridgman method), a zone melting method (a zone leveling method and a floating zone method), a special growth method (a VLS method and a liquid phase epitaxy method) and the like.

Preferable examples of the crystallization method include a method of dissolving compound (I) in a suitable solvent (e.g., alcohols such as methanol, ethanol, etc. and the like) at a temperature of 20 to 120°C, and cooling the resulting solution to a temperature not higher than the temperature of dissolution (e.g., 0 to 50°C, preferably 0 to 20°C) and the like.

The thus obtained crystals of the present invention can be isolated, for example, by filtration and the like.

As the analysis method of the obtained crystals, crystal analysis by powder X-ray diffraction is generally performed. Moreover, as a method for determining the crystal direction, a mechanical method, an optical method and the like can also be mentioned.

The crystals of compound (I) obtained by the above-mentioned production method (hereinafter to be abbreviated as the "crystal of the present invention") has high purity and high quality, and low hygroscopicity, is not denatured even after a long-term preservation under general conditions, and is extremely superior in the stability. Moreover, the crystal is superior in biological properties (e.g., pharmacokinetics (absorption, distribution, metabolism, excretion), efficacy expression, etc.), and thus it is extremely useful as a pharmaceutical composition.

In the present specification, the specific rotation ($[\alpha]_D$) means that measured using, for example, polarimeter (JASCO Corporation (JASCO), P-1030 polarimeter (No.AP-2)) and the like.

In the present specification, the melting point means that measured using, for example, a micromelting point apparatus (Yanako, MP-500D) or a DSC (differential scanning calorimetry) device (SEIKO, EXSTAR 6000) and the like.

In the present specification, the peak by powder X-ray diffraction means that measured using, for example, RINT Ultima$^+$ 2100 (Rigaku Corporation), etc. with a Cu-Kα ray as a ray source.

In general, the melting points and the peak by powder X-ray diffraction may vary depending on the measurement apparatuses, the measurement conditions and the like. The crystal in the present specification may show different values from the melting point or the peak by powder X-ray diffraction described in the present specification, as long as it is within each of a general error range.

The compound of the present invention has excellent antagonistic action for a tachykinin receptor, particularly substance P receptor antagonistic action including the inhibitory action for the increased permeability of blood vessel of a trachea induced by capsaicin, neurokinin A receptor antagonistic action. The compound of the present invention has low toxicity and thus it is safe.

Accordingly, the compounds of the present invention having excellent antagonistic actions for substance P receptors and neurokinin A receptors, etc. can be used as a safe pharmaceutical composition for preventing and treating the following diseases related to substance P in mammals (e.g., mice, rats, hamsters, rabbits, cats, dogs, bovines, sheep, monkeys, humans, etc.).

(1) Lower urinary tract diseases [for example, overactive bladder, stress urinary incontinence, mixed urinary incontinence, lower urinary tract symptoms accompanied by prostatic hyperplasia, pelvic visceral pain, lower urinary tract symptoms accompanied by chronic prostatitis, abnormal urination such as lower urinary tract symptoms accompanied by interstitial cystitis, etc.]

(2) Gastrointestinal diseases [for example, irritable bowel syndrome, inflammatory bowel disease, ulcerative colitis syndrome, Crohn's disease, diseases caused by a spiral urease-positive gram-negative bacterium (e.g., *Helicobacter pylori*, etc.) (e.g., gastritis, gastric ulcer, etc.), gastric cancer, postgastrostomy disorder, dyspepsia, esophageal ulcer, pancreatitis, polyp of the colon, cholelithiasis, hemorrhoids, peptic ulcer, situational ileitis, vomiting, nausea, motion sickness, anorexia, bulimia, constipation, diarrhea, borborygmi, etc.]

(3) Inflammatory or allergic diseases [for example, allergic rhinitis, conjunctivitis, gastrointestinal

allergy, pollinosis, anaphylaxis, dermatitis, herpes, psoriasis, bronchitis, expectoration, retinopathy, postoperative and posttraumatic inflammation, regression of puffiness, pharyngitis, cystitis, meningitidis, inflammatory ophthalmic diseases, etc.]

(4) Osteoarthropathy diseases [for example, rheumatoid arthritis (chronic rheumatoid arthritis), arthritis deformans, rheumatoid myelitis, osteoporosis, abnormal growth of cells, bone fracture, bone refracture, osteomalacia, osteopenia, osseous Behcet's disease, rigid myelitis, articular tissue destruction by gonarthrosis deformans and similar diseases thereto, etc.]

(5) Respiratory diseases [for example, cold syndrome, pneumonia, asthma, pulmonary hypertension, pulmonary thrombi/pulmonary obliteration, pulmonary sarcoidosis, pulmonary tuberculosis, interstitial pneumonia, silicosis, adult tachypnea syndrome, chronic obliterative pulmonary diseases, cough, etc.]

(6) Infectious diseases [HIV infectious diseases, virus infectious diseases due to cytomegalo virus, influenza virus, herpes virus and the like, rickettsia infectious diseases, bacterial infectious diseases, sexually-transmitted diseases, carinii pneumonia, *helicobacter pylori* infectious disease, systemic fungal infectious diseases, tuberculosis, invasive staphylococcal infectious diseases, acute viral encephalitis, acute bacterial meningitidis, AIDS encephalitis, septicemia, sepsis, sepsis gravis, septic shock, endotoxin shock, toxic shock syndromes, etc.]

(7) Cancers [for example, primary, metastatic or recurrent breast cancer, prostatic cancer, pancreatic cancer, gastric cancer, lung cancer, colorectal cancer (colon cancer, rectal cancer, anal cancer), esophagus cancer, duodenal cancer, head and neck cancer (tongue

cancer, pharynx cancer, larynx cancer), brain tumor, neurinoma, non-small cell lung cancer, small cell lung cancer, hepatic cancer, renal cancer, colic cancer, uterine cancer (cancer of the uterine body, uterine cervical cancer), ovarian cancer, bladder cancer, skin cancer, hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer, bone tumor, hemangioma, angiofibroma, retinosarcoma, penis cancer, pediatric solid cancer, Kaposi's sarcoma, Kaposi's sarcoma caused by AIDS, tumor of the maxillary sinus, fibrous histiocytoma, smooth muscle sarcoma, rhabdomyosarcoma, liposarcoma, fibroid tumors of the uterus, osteoblastoma, osteosarcoma, chondrosarcoma, carcinomatous mesothelial tumor, tumors such as leukemia, Hodgkin's disease, etc.]

(8) Central nerve diseases [for example, neurodegenerative diseases (e.g., Alzheimer's disease, Down's disease, Parkinson's disease, Creutzfeldt-Jakob's disease, amyotrophic lateral sclerosis (ALS), Huntington chorea, diabetic neuropathy, multiple sclerosis, etc.), mental diseases (e.g., schizophrenia, depression, mania, anxiety neurosis, obsessive-compulsive neurosis, panic disorder, epilepsy, alcohol dependence, anxiety symptom, anxious mental state, dysthymia, cyclothymia, nervous hypersensitivity, autism, syncope, addiction, decreased libido, etc.), central and peripheral nerve disorders (e.g., head trauma, spinal cord injury, brain edema, disorders of sensory function, abnormality of sensory function, disorders of autonomic nervous function and abnormality of autonomic nervous function, whiplash injury, etc.), memory disorders (e.g., senile dementia, amnesia, cerebrovascular dementia, etc.), cerebrovascular disorders (e.g., disorders and aftereffect and/or complication from intracerebral hemorrhage, brain

infarction, etc, asymptomatic cerebro-vascular accident, transient cerebral ischemic attack, hypertensive encephalopathia, blood-brain barrier disorder, etc.), recurrence and aftereffect of cerebro-vascular accident (e.g., neural symptoms, mental symptoms, subjective symptoms, disorders of daily living activities, etc.), post-cerebrovascular occlusion central hypofunction; disorder or abnormality of cerebral circulation and/or autoregulation of renal circulation], sleep disorder

(9) Circulatory diseases [for example, acute coronary artery syndromes (e.g., acute cardiac infarction, unstable angina, etc.), peripheral arterial obstruction, Raynaud's disease; Buerger disease; restenosis after coronary-artery intervention (percutaneous transluminal coronary angioplasty (PTCA), directional coronary atherectomy (DCA), stenting, etc.), restenosis after coronary-artery bypass operation, restenosis after intervention (angioplasty, atherectomy, stenting, etc.) or bypass operation in other peripheral artery, ischemic cardiac diseases (e.g., cardiac infarction, angina, etc.), myocarditis, intermittent claudication, lacunar infarction, arteriosclerosis (e.g., atherosclerosis, etc.), cardiac failure (acute cardiac failure, chronic cardiac failure accompanied by congestion), arrhythmia, progress of atherosclerotic plaque, thrombosis, hypertension, hypertensive tinnitus; hypotension, etc.]

(10) Pains [e.g., pelvic visceral pain including headache, migraine, neuralgia, cystodynia, etc.]

(11) Autoimmune diseases [for example, collagen disease, systemic lupus erythematosus, scleroderma, polyarteritis, myasthenia gravis, multiple sclerosis, Sjogren's syndrome, Behcet's disease, etc.]

(12) Hepatic diseases [e.g., hepatitis (including chronic hepatitis), cirrhosis, interstitial hepatic

diseases, etc.]

(13) Pancreatic diseases [e.g., pancreatitis (including chronic pancreatitis), etc.]

(14) Renal diseases [e.g., nephritis, glomerulonephritis, glomerulosclerosis, renal failure, thrombotic microangiopathy, dialysis complications, organ disorders including nephropathia by radiation, diabetic nephropathy, etc.]

(15) Metabolic diseases [e.g., diabetic diseases (insulin-dependent diabetes, diabetic complications, diabetic retinopathy, diabetic microangiopathy, diabetic neuropathy, etc.); impaired glucose tolerance, obesity, benign prostatic hypertrophy, sexual dysfunction, etc.]

(16) Endocrine diseases [e.g., Addison's disease, Cushing's syndrome, melanocytoma, primary aldosteronism, etc.]

(17) Other diseases

(a) Transplant rejection [e.g., posttransplantational rejection, posttransplantational polycythemia, hypertension, organ disorder and/or vascular hypertrophy, graft-versus-host disease, etc.]

(b) Abnormality in characteristic of blood and/or blood components [e.g., enhancement in platelet aggregation, abnormality of erythrocyte deformability, enhancement in leukocyte adhesiveness, increase in blood viscosity, polycythemia, vascular peliosis, autoimmune hemolytic anemia, disseminated intravascular coagulation syndrome (DIC), multiple myelopathy, etc.]

(c) Gynecologic diseases [e.g., climacteric disorder, gestational toxicosis, endometriosis, hysteromyoma, ovarian disease, mammary disease, premenstrual syndrome, etc.]

(d) Dermatic diseases [e.g., keloid, angioma, psoriasis, pruritus, etc.]

(e) Ophthalmic diseases [e.g., glaucoma, ocular hypertension disease, etc.]

(f) Otolaryngological diseases [e.g., Menuel syndrome, tinnitus, gustation disorder, dizziness, disequilibrium, dysphagia, etc.]

(g) Diseases due to environmental and/or occupational factors (e.g., radiation disorder, disorders by ultraviolet ray, infrared ray or laser ray, altitude sickness, etc.)

(h) Ataxia, rigidity, tremor, dyskinesia, akinesia

(i) Chronic fatigue syndrome

(j) sudden infant death syndrome

(k) hiccup (singultus)

(l) disease causing palpitation, vertigo, heartburn and the like

Of these diseases, the compound of the present invention is particularly useful as a tachykinin receptor antagonist, as an agent for ameliorating and treating symptoms of lower urinary tract such as urinary frequency, urinary incontinence, etc., as an agent for the prophylaxis or treatment of gastrointestinal disease and as an agent for the prophylaxis or treatment of central nervous system disease. Particularly, it is useful as an agent for the prophylaxis or treatment of overactive bladder, irritable bowel syndrome, inflammatory bowel disease, vomiting, nausea, depression, anxiety neurosis, anxiety symptom, pelvic visceral pain or interstitial cystitis.

The pharmaceutical preparations comprising the compound of the present invention may be in any solid forms of powders, granules, tablets, capsules, suppositories, etc., and in any liquid forms of syrups, emulsions, injections, suspensions, etc.

The pharmaceutical preparations including the compound of the present invention can be produced by any conventional methods, for example, blending, kneading, granulation, tabletting, coating, sterilization, emulsification, etc., in accordance with the forms of the preparations to be produced. For the production of such pharmaceutical preparations, for example, each of the items in General Principles for pharmaceutical preparations in the Japanese Pharmacopeia, can be made reference to. In addition, the pharmaceutical preparations of the present invention may be formulated into a sustained release preparation containing active ingredients and biodegradable polymer compounds. The sustained release preparation can be produced according to the method described in JP-A-9-263545.

In the pharmaceutical preparations of the present invention, the content of the compound or a salt thereof in the present invention varies depending on the forms of the preparations, but is generally about 0.01 to 100% by weight, preferably about 0.1 to 50% by weight, more preferably about 0.5 to 20% by weight, relative to the total weight of each preparation.

When the compound of the present invention is used in the above-mentioned pharmaceutical preparations, it may be used alone, or in admixture with a suitable, pharmaceutically acceptable carrier, for example, excipients (e.g., starch, lactose, sucrose, calcium carbonate, calcium phosphate, etc.), binders (e.g., starch, arabic gum, carboxymethyl cellulose, hydroxypropyl cellulose, crystalline cellulose, alginic acid, gelatin, polyvinyl pyrrolidone, etc.), lubricants (e.g., stearic acid, magnesium stearate, calcium stearate, talc, etc.), disintegrants (e.g., calcium carboxymethylcellulose, talc, etc.), diluents (e.g., water for injection, physiological saline, etc.) and if desired, with the additives (e.g., a stabilizer, a preservative, a colorant, a fragrance, a dissolution aid, an emulsifier, a buffer, an isotonic agent, etc.) and the like, by ordinary methods. It can be formulated into the solid preparations such as powders, fine granules, granules, tablets, capsules, etc., or into the liquid preparations such as injections, etc., and can be administered orally or parenterally.

The dose varies depending on the kinds of the compound of the present invention or a pharmaceutically acceptable salt thereof, the administration route, the condition and the age of patients, etc. For example, the dose for oral administration of the pharmaceutical preparation to an adult patient suffering from abnormal urination is generally from about 0.005 to 50 mg/kg body/day, preferably from about 0.05 to 10 mg/kg body/day, more preferably from about 0.2 to 4 mg/kg body/day, based on the compound of the present invention, which may be administered once a day or in two or three divided portions a day.

The dose when the pharmaceutical composition of the present invention is a sustained release preparation varies depending on the kinds and the content of compound (I), the formulation, the duration time of drug release, the animals to be administered (e.g., mammals such as humans, rats, mice, cats, dogs, rabbits, bovines, swines, etc.), and the object of administration. For example, when it is parenterally administered, preferably about 0.1 to about 100 mg of compound (I) may be released from the preparation for 1 week.

The compound of the present invention can be used in a mixture or combination with other pharmaceutically active ingredients at a suitable ratio.

Combination of the compound of the present invention with other pharmaceutically active

ingredients can give the following excellent effects:
(1) a dose can be reduced as compared with separate administration of the compound of the present invention or other pharmaceutically active ingredients. More specifically, when the compound of the present invention is combined with anticholinergic agents or NK-2 receptor antagonists, the dose can be reduced as compared with separate administration of anticholinergic agents or NK-2 receptor antagonists, and therefore, side effects such as dry mouth can be reduced;
(2) according to symptoms of patient (mild symptoms, severe symptoms, etc.), a drug to be combined with the compound of the present invention can be selected;
(3) by choosing other pharmaceutically active ingredients which have different mechanism of action from that of the compound of the present invention, the therapeutic period can be designed longer;
(4) by choosing other pharmaceutically active ingredients which have different mechanism of action from that of the compound of the present invention, continuation of therapeutic effects can be obtained; and
(5) by combining the compound of the present invention and other pharmaceutically active ingredients, excellent effects such as synergic effects can be obtained.

A drug which is mixed or combined with the compound of the present invention (hereinafter, briefly referred to as combination drugs) includes the following:

(1) Agent for treating diabetes

Insulin preparations (e.g., animal insulin preparations extracted from the bovine or swine pancreas; human insulin preparations synthesized by a genetic engineering technique using *Escherichia coli* or a yeast; insulin zinc; protamine zinc insulin; a fragment or a derivative of insulin (e.g., INS-1, etc.), agents for potentiating insulin sensitivity (e.g., pioglitazone hydrochloride, troglitazone, rosiglitazone or its maleate, JTT-501, MCC-555, YM-440, GI-262570, KRP-297, FK-614, CS-011, etc.), α-glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate, etc.), biguanides (e.g., phenformin, metformin, buformin, etc.), sulfonylureas (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, etc.) and other insulin secretagogues (e.g., repaglinide, senaglinide, mitiglinide or its calcium salt hydrate, GLP-1, nateglinide, etc.), dipeptidylpeptidase IV inhibitors (e.g., vildagliptin, sitagliptin, saxagliptin, alogliptin, NVP-DPP-728, PT-100, P32/98, etc.), β_3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, AJ-9677, AZ40140, etc.), amylin agonists (e.g., pramlintide, etc.), phosphotyrosine phosphatase inhibitors (e.g., vanadic acid, etc.), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, etc.), SGLT (sodium-glucose cotransporter) inhibitors (e.g., T-1095, etc.) and the like.

(2) Agent for treating diabetic complications

Aldose reductase inhibitors (e.g., tolrestat, epalrestat, zenarestat, zopolrestat, fidarestat (SNK-860), minalrestat (ARI-509), CT-112, etc.), neurotrophic factors (e.g., NGF, NT-3, etc.), AGE inhibitors (e.g., ALT-945, pimagedine, pyratoxathine, N-phenacylthiazolium bromide (ALT-766), EXO-226, etc.), active oxygen scavengers (e.g., thioctic acid, etc.), cerebral vasodilators (e.g., tiapuride, etc.) and the like.

(3) Antihyperlipidemic agent

Statin compounds inhibiting cholesterol synthesis (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin or their salt (e.g., sodium salt, etc.) and the like), squalene synthase inhibitors or fibrate compounds having triglyceride lowering action (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate, etc.) and the like.

(4) Hypotensive agent

Angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril, etc.), angiotensin II antagonists (e.g., losartan, candesartan cilexetil, etc.), calcium antagonists (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine, etc.), clonidine, and the like.

(5) Antiobesity agent

Antiobesity drugs acting on the central nervous system (e.g. dexfenfluramine, fenfluramine, phentermine, sibutramine, anfepramone, dexamphetamine, mazindol, phenylpropanolamine, clobenzorex, etc.), pancreatic lipase inhibitors (e.g. orlistat, etc.), β_3 agonists (e.g. CL-316243, SR-58611-A, UL-TG-307, AJ-9677, AZ40140, etc.), anorectic peptides (e.g. leptin, CNTF (Ciliary Neurotrophic Factor), etc.), cholecystokinin agonists (e.g. lintitript, FPL-15849, etc.).

(6) Diuretic agent

Xanthine derivatives (e.g., theobromine sodium salicylate, theobromine calcium salicylate, etc.), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide, etc.), antialdosterone preparations (e.g., spironolactone, triamterene, etc.), carbonic anhydrase inhibitors (e.g., acetazolamide, etc.), chlorobenzenesulfonamide preparations (e.g., chlorthalidone, mefruside, indapamide, etc.), azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide, furosemide, etc.

(7) Chemotherapeutic agent

Alkylating agents (e.g., cyclophosphamide, ifosfamide, etc.), metabolic antagonists (e.g., methotrexate, 5-fluorouracil, etc.), antitumor antibiotics (e.g., mitomycin, adriamycin, etc.), plant-derived antitumor agents (e.g., vincristine, vindesine, taxol, etc.), cisplatin, carboplatin, etoposide, etc. Among these, 5-fluorouracil derivatives such as Furtulon and Neo-Furtulon are preferred.

(8) Immunotherapeutic agent

Microorganism- or bacterium-derived components (e.g., muramyl dipeptide derivatives, Picibanil, etc.), immunopotentiator polysaccharides (e.g., lentinan, schizophyllan, krestin, etc.), genetically engineered cytokines (e.g., interferons, interleukins (IL), etc.), colony stimulating factors (e.g., granulocyte colony stimulating factor, erythropoietin, etc.) and the like. Among these, interleukins such as IL-1, IL-2, IL-12, etc. are preferred.

(9) Therapeutic agent recognized to ameliorate cachexia in animal models or clinical practice

Progesterone derivatives (e.g., megestrol acetate) [Journal of Clinical Oncology, vol. 12, pp. 213-225, 1994], metoclopramide pharmaceuticals, tetrahydrocannabinol pharmaceuticals (the above reference is applied to both), fat metabolism ameliorating agents (e.g., eicosapentanoic acid) [British Journal of Cancer, vol. 68, pp. 314-318, 1993], growth hormones, IGF-1, and antibodies to the cachexiainducing factors such as TNF-α, LIF, IL-6 and oncostatin M.

(10) Antiinflammatory agent

Steroids (e.g., dexamethasone, etc.), sodium hyaluronate, cyclooxygenase inhibitors (e.g., indomethacin, ketoprofen, loxoprofen, meloxicam, ampiroxicam, celecoxib, rofecoxib, etc.) and the like.

(11) Miscellaneous

Glycosylation inhibitors (e.g., ALT-711, etc.), nerve regeneration promoting drugs (e.g., Y-128, VX853, prosaptide, etc.), drugs acting on the central nervous system (e.g., antidepressants such as desipramine, amitriptyline, imipramine, fluoxetine, paroxetine, doxepin, duloxetine, venlafaxine, etc.), anticonvulsants (e.g., lamotrigine, carbamazepine, gabapentin), antiarrhythmic drugs (e.g., mexiletine), acetylcholine receptor ligands (e.g., ABT-594), endothelin receptor antagonists (e.g., ABT-627), monoamine uptake inhibitors (e.g., tramadol), indoleamine uptake inhibitors (e.g., fluoxetine, paroxetine), narcotic analgesics (e.g., morphine), non-narcotic analgesics (e.g., buprenorphine, axomadol), GABA receptor agonists, GABA uptake inhibitors (e.g., tiagabine), α_2 receptor agonists (e.g., clonidine), local analgesics (e.g., capsaicin), protein kinase C inhibitors (e.g., LY-333531), antianxiety drugs (e.g., benzodiazepines), phosphodiesterase inhibitors (e.g., sildenafil), dopamine receptor agonists (e.g., apomorphine), dopamine receptor antagonists (e.g., haloperidol), serotonin receptor agonists (e.g., tandospirone citrate, sumatryptan, tegaserod), serotonin receptor antagonists (e.g., cyproheptadine hydrochloride, ondansetron), serotonin uptake inhibitors (e.g., fluvoxamine maleate, fluoxetine, paroxetine), hypnotics (e.g., triazolam, zolpidem), anticholinergic agents, α_1 receptor blocking agents (e.g., tamsulosin, urapidil, naftopidil, silodosin), muscle relaxants (e.g., baclofen, etc.), potassium channel openers (e.g., nicorandil), calcium channel blocking agents (e.g., nifedipine), chloride channel openers (e.g., lubiprostone), agents for preventing and/or treating Alzheimer's disease (e.g., donepezil, rivastigmine, galanthamine), agents for treating Parkinson's disease (e.g., L-dopa), agents for preventing and/or treating multiple sclerosis (e.g., interferon β-1a), histamine H_1 receptor inhibitors (e.g., promethazine hydrochloride), proton pump inhibitors (e.g., lansoprazole, omeprazole), antithrombotic agents (e.g., aspirin, cilostazol), NK-2 receptor antagonists, NK-3 receptor antagonists (e.g., talnetant), agents of treating HIV infection (saquinavir, zidovudine, lamivudine, nevirapine), agents of treating chronic obstructive pulmonary diseases (salmeterol, thiotropium bromide, cilomilast), diuretics (e.g., furosemide), antidiuretics (e.g., vasopressin V2 receptor agonists), etc.

Anticholinergic agents include, for example, atropine, scopolamine, homatropine, tropicamide, cyclopentolate, butylscopolamine bromide, propantheline bromide, methylbenactyzium bromide, mepenzolate bromide, flavoxate, pirenzepine, ipratropium bromide, trihexyphenidyl, oxybutynin, propiverine, darifenacin, tolterodine, solifenacin, temiverine, trospium chloride or a salt thereof (e.g., atropine sulfate, scopolamine hydrogen bromide, homatropine hydrogen bromide, cyclopentolate hydrochloride, flavoxate hydrochloride, pirenzepine hydrochloride, trihexyphenidyl hydrochloride, oxybutynin chloride, tolterodine tartrate, solifenacin succinate, etc.), preferably, oxybutynin, propiverine, darifenacin, tolterodine, solifenacin, temiverine, trospium chloride or a salt thereof (e.g., oxybutynin chloride, tolterodine tartrate, solifenacin succinate, etc.). In addition, acetylcholinesterase inhibitors (e.g., distigmine, etc.) and the like can be used.

NK-2 receptor antagonists include, for example, a piperidine derivative such as GR159897, GR149861, SR48968 (saredutant), SR144190, YM35375, YM38336, ZD7944, L-743986, MDL105212A, ZD6021, MDL105172A, SCH205528, SCH62373, R-113281, etc., a perhydroisoindole derivative such as RPR-106145, etc., a quinoline derivative such as SB-414240, etc., a pyrrolopyrimidine derivative such as ZM-253270, etc., a pseudopeptide derivative such as MEN11420 (nepadutant), SCH217048, L-659877, PD-147714 (CAM-2291), MEN10376, S16474, etc., and others such as GR100679, DNK333, GR94800, UK-224671, MEN10376, MEN10627, or a salt thereof, and the like.

The pharmaceutical composition comprising a mixture or combination of the compound of the present invention and the concomitant drugs may be formulated into

(1) a single formulation as a pharmaceutical composition containing the compound of the present invention and the concomitant drugs, or

(2) a formulation comprising the compound of the present invention and the concomitant drugs which are separately formulated. Hereinafter, it is generally briefly referred to as the combination preparation of the present invention.

The combination preparation of the present invention can be formulated by mixing the compound of the present invention and active ingredients of the concomitant drugs separately or at the same time as itself or with pharmaceutically acceptable carriers in the same manner as in the aforementioned method of producing the pharmaceutical preparation comprising the compound of the present invention.

A daily dose of the combination preparation of the present invention varies depending on severity of the symptoms, age, sex, weight and sensitivity of the subject to be administered, time and interval of administration, property, formulation and kinds of pharmaceutical preparation, kinds of active ingredients, etc., and is not particularly limited. The dose in terms of the compound of the present invention is not particularly limited if it causes no problems of side effects. In the case of oral administration, a daily dosage is usually in a range of about 0.005 to 100 mg, preferably about 0.05 to 50 mg, and more preferably about 0.2 to 30 mg, per 1 kg body weight of mammals, which may be administered once a day or in two or three divided portions a day.

The dose of the compound or the combination preparation of the present invention may be set within the range such that it causes no problems of side effects. The daily dose as the compound or the combination preparation of the present invention varies depending on severity of symptoms, age, sex, weight and sensitivity of the subject to be administered, time and interval of administration, property, formulation and kinds of pharmaceutical preparation, kinds of active ingredients, etc., and is not particularly limited. In the case of oral administration, a daily dosage in terms of active ingredients is usually in the order of about 0.001 to 2000 mg, preferably about 0.01 to 500 mg, and more preferably about 0.1 to 100 mg, per 1 kg body weight of mammals, which may be administered once a day or in two to four divided portions a day.

In administering the combination preparation of the present invention, the compound of the present invention and the combination drugs may be administered at the same time or, the combination drugs may be administered before administering the compound of the present invention, and vice versa. In case of staggered administration, the time interval varies depending on the active ingredients to be administered, a formulation and an administration route. For example, if the combination drugs are administered first, the compound of the present invention may be administered 1 minute to 3 days, preferably 10 min to 1 day, more preferably 15 min to 1 hr after administering the combination drugs. If the compound of the present invention is administered first, the combination drugs may be administered 1 minute to 1 day, preferably 10 min to 6 hrs, more preferably 15 min to 1 hr after administering the compound of the present invention.

In a preferred administration method, about 0.001 to 200 mg/kg of the combination drugs formulated as an oral preparation is administered orally and then after about 15 minutes, about 0.005 to 100 mg/kg of the compound of the present invention formulated as an oral preparation is administered orally as a daily dose.

In the combination preparation of the present invention, the content of the compound of the present invention varies depending on the forms of the preparation, but usually in the order of 0.01 to 100 wt%, preferably 0.1 to 50 wt%, and further preferably 0.5 to 20 wt%, relative to the total preparation.

Examples

The present invention is further described in detail in with reference to Reference Examples, Examples, Preparative Examples and Experimental Examples, which are not intended to restrict the invention and may be modified without departing from the scope of the invention.

Elution in the column chromatography in the following Reference Examples and Examples was conducted under observation by TLC (thin layer chromatography), unless otherwise specifically indicated. In the TLC observation, 60F254, TLC plates, produced by Merck & Co., Inc. was used, and the solvent employed as an elution solvent in the column chromatography was used as an eluent. For the detection, a UV detector was used. As silica gel for the column chromatography, Silica Gel 60 (70 to 230 mesh) produced by Merck & Co., Inc. was used. The "room temperature" referred herein means temperature generally from about 10°C to 35°C. For drying extract, sodium sulfate or magnesium sulfate was used.

The abbreviations in Examples and Reference Examples mean the following.

LC: liquid chromatography
MS: mass spectrometry
ESI: electrospray ionization
FAB: fast atom bombardment
M: molecular ion peak
NMR: nuclear magnetic resonance
Hz: hertz
J: coupling constant
m: multiplet
q: quartet
t: triplet
d: doublet
s: singlet
br: broad
dt: double triplet
brs: broad singlet
Ac: acetyl group

^{t}Bu: tert-butyl group
Boc: tert-butyloxycarbonyl group
Et: ethyl group
Ph: phenyl group
N: normal concentration
MPa: megapascal
DMF: N,N-dimethylformamide
THF: tetrahydrofuran
DMSO: dimethyl sulfoxide
IPE: diisopropyl ether
HOBt·H_2O: 1-hydroxybenzotriazole hydrate
WSC·HCl: 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride

LC-MS in Examples and Reference Examples were measured under the following conditions.

Analysis by LC-MS
Instrument: Waters LC-MS system
HPLC system: Agilent HP1100
MS system: Micromass ZMD
HPLC conditions

Column: CAPCELL PAK C18UG120, S-3 µm, 1.5×35 mm (Shiseido)

Solvents: Solution A; water containing 0.05% trifluoroacetic acid, Solution B; acetonitrile containing 0.05% trifluoroacetic acid

Gradient cycles: 0.00 min (Solution A/Solution B =90/10), 2.00 min (Solution A/Solution B =5/95), 2.75 min (Solution A/Solution B =5/95), 2.76 min (Solution A/Solution B =90/10), 3.60 min (Solution A/Solution B =90/10)

Injection volume: 2 µL, Flow rate: 0.5 mL/min, Detection method: UV 220 nm

MS conditions
Ionization method: ESI

Reference Example 1

4-(5-formyl-6-methoxypyridin-3-yl)benzonitrile

A mixture of 5-bromo-2-methoxynicotinaldehyde (2.0 g) synthesized by a known method (Journal of Heterocyclic Chemistry 1985, 22(6), 1583-1592), (4-cyanophenyl)boronic acid (1.36 g), $Pd(PPh_3)_4$ (0.32 g) and potassium carbonate (2.6 g) in THF (20 mL) and water (10 mL) was heated under reflux for 12 hrs. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and concentrated under reduced pressure. The obtained residue was crystallized from acetone/ethanol/IPE to give the title compound (0.93 g) as white crystals.

melting point: 157°C

Reference Example 2

2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]nicotinaldehyde

(step 1)

To a solution of 6-methoxypyridine-3-amine (24.8 g) and Et_3N (26.3 g) in methylene chloride (250 mL) was added trifluoroacetic anhydride (48.3 g) at 0°C, and the mixture was stirred at room temperature for 2 hrs. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from acetone/IPE/hexane to give 2,2,2-trifluoro-N-(6-methoxypyridin-3-yl)acetamide (37.0 g, 84%) as white crystals.

melting point: 108°C

(step 2)

To a solution of the compound obtained in step 1

(22.0 g) in carbon tetrachloride (300 mL) was added triphenyl phosphine (39.3 g), and the mixture was stirred at 95°C for 20 hrs. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in DMF (250 mL), and sodium azide (10.4 g) was added at 0°C. The reaction mixture was stirred at room temperature for 30 min, water (200 mL) was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous ammonium chloride solution, and then brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→50% ethyl acetate/hexane) to give 2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]pyridine (22.8 g, 93%) as pale-yellow crystals.

melting point: 49°C

(step 3)

To a solution of the compound obtained in step 2 (4.9 g) in acetic acid (15 mL) was added sodium acetate (1.65 g), the mixture was stirred for 10 min and bromine (4.8 g) was added at room temperature. The reaction mixture was stirred at 80°C for 14 hrs, water (40 mL) was added, and the mixture was extracted with methylene chloride. The organic layer was washed with 1N aqueous sodium hydroxide solution and 1N aqueous sodium thiosulfate solution, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→30% ethyl acetate/hexane) and crystallized from IPE/hexane to give 3-bromo-2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]pyridine (0.40 g, 6%) as white crystals.

melting point: 106°C

(step 4)

A solution of the compound obtained in step 3 (2.32 g) and zinc cyanide (0.84 g) in DMF (15 mL) was added $Pd(PPh_3)_4$ (0.41 g), and the mixture was stirred at 110°C under an argon atmosphere for 10 hrs. Then $Pd(PPh_3)_4$ (0.41 g) was added, and the mixture was stirred at 110°C under an argon atmosphere for 10 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous ammonium chloride solution, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→50% ethyl acetate/hexane) and crystallized from IPE/hexane to give 2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]nicotinonitrile (1.3 g, 67%) as white crystals.

melting point: 80-82°C

(step 5)

To a mixture of the compound obtained in step 4 (1.35 g) and Raney-nickel (about 7 g) in pyridine (15 mL)-acetic acid (7.5 mL)-water (7.5 mL) was added $NaH_2PO_2 \cdot H_2O$ (5 g), and the mixture was stirred at 40°C for 1.5 hrs. The catalyst was removed by decantation, and the reaction mixture was acidified with 2N hydrochloric acid. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with 2N hydrochloric acid and brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→50% ethyl acetate/hexane) and crystallized from IPE/hexane to give the title compound (0.25 g, 18%) as white crystals.

melting point: 96-98°C

Reference Example 3

4-(6-formyl-5-methoxypyridin-2-yl)benzonitrile

(step 1)

A solution of 3-hydroxypicolinic acid (50.9 g) and conc. sulfuric acid (40 mL) in methanol (500 mL) was heated under reflux for 5 days. The reaction mixture was concentrated under reduced pressure, and the residue was poured into cold water. The mixture was basified with potassium carbonate, and extracted twice with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→50% ethyl acetate/hexane) and crystallized from ethyl acetate/hexane to give methyl 3-hydroxypyridine-2-carboxylate (35.5 g, 64%) as white crystals.

(step 2)

To a solution of the compound obtained in step 1 (9.19 g) in water (150 mL) was added bromine (3.23 mL) at room temperature and the mixture was stirred for 4 hrs. The reaction mixture was extracted with a mixture of ethyl acetate/THF, and the organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was crystallized from ethyl acetate/hexane to give methyl 6-bromo-3-hydroxypyridine-2-carboxylate (10.3 g, 74%) as brown crystals.

(step 3)

A solution of the compound obtained in step 2 (9.42 g), methyl iodide (2.78 mL) and potassium carbonate (7.29 g) in DMF (80 mL) was stirred at room temperature for 4 hrs, and poured into cold water. The mixture was extracted twice with ethyl acetate, and the organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 20→25% ethyl acetate/hexane) and crystallized from ethyl acetate/hexane to give methyl 6-bromo-3-methoxypyridine-2-carboxylate (7.57 g, 76%) as white crystals.

(step 4)

To a solution of the compound obtained in step 3 (7.56 g) in THF (110 mL) was added diisobutylaluminum hydride (DIBAL-H) (1.5M toluene solution, 24.6 mL) at -78°C, and the mixture was stirred at -78°C for 1 hr. To the reaction mixture was added saturated aqueous Rochelle salt, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→33% ethyl acetate/hexane) and crystallized from ethyl acetate/hexane to give 6-bromo-3-methoxypyridine-2-carbaldehyde (5.36 g, 81%) as white crystals.

(step 5)

A mixture of the compound obtained in step 4 (1.08 g), (4-cyanophenyl)boronic acid (0.96 g), $Pd(PPh_3)_4$ (0.29 g) and potassium carbonate (1.04 g) in THF (25 mL) and water (5 mL) was heated under reflux for 12 hrs. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (solvent gradient; 0→50% ethyl acetate/hexane) and crystallized from ethyl acetate/hexane to give 4-(6-formyl-5-methoxypyridin-2-yl)benzonitrile (0.43 g, 36%) as white crystals.

^{1}H-NMR (300MHz, $CDCl_3$): δ4.05(3H, s), 7.54 (1H, d, J=9.0Hz), 7.76-7.79 (2H, m), 7.98 (1H, d, J=8.0Hz), 8.14-8.17 (2H, m), 10.36 (1H, s)

Reference Example 4

3-methoxy-1-phenyl-1H-pyrazole-4-carbaldehyde

(step 1)

To a solution of N′-phenylacetohydrazide (17.0 g) in phosphorus oxychloride (104 g) was added diethyl ethoxymethylenemalonate (24.5 g) at room temperature, and the mixture was stirred at 70°C for 3 hrs. The reaction mixture was cooled by pouring into water and the precipitate was collected by filtration. The precipitate was washed with water, dissolved in ethyl acetate, and the mixture was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (solvent; ethyl acetate) and crystallized from ethyl acetate/hexane to give ethyl 3-hydroxy-1-phenyl-1H-pyrazole-4-carboxylate (3.67 g, 14%) as pale-yellow crystals.

(step 2)

To a solution of the compound obtained in step 1 (0.70 g) and K_2CO_3 (0.58 g) in DMF (12 mL) was added methyl iodide (0.224 mL), and the mixture was stirred at room temperature for 4 hrs. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N $KHSO_4$ and brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→20% ethyl acetate/hexane) and crystallized from ethyl acetate/hexane to give ethyl 3-methoxy-1-phenyl-1H-pyrazole-4-carboxylate (0.48 g, 65%) as white crystals.

(step 3)

To a mixture of the compound obtained in step 2 (0.44 g) in Et_2O (6 mL) and THF (4 mL) was added DIBAL-H (1.5M toluene solution, 2.6 mL) at -78°C, and the mixture was stirred at -10°C for 4 hrs. A saturated aqueous Rochelle salt was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→33% ethyl acetate/hexane) to give (3-methoxy-1-phenyl-1H-pyrazol-4-yl)methanol (0.32 g, 88%) as colorless oil.

(step 4)

To a solution of the compound obtained in step 3 (0.31 g) and Et_3N (0.64 mL) in methylene chloride (5 mL) was added a solution of SO_3-pyridine complex (0.72 g) in DMSO (5 mL) at 0°C, and the mixture was stirred at room temperature for 2 hrs. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 10→25% ethyl acetate/hexane) to give the title compound (0.046 g, 15%) as white crystals.

^{1}H-NMR (300MHz, $CDCl_3$): δ 4.10 (3H, s), 7.30-7.35 (2H, m), 7.43-7.49 (2H, m), 7.63-7.67 (2H, m), 8.24 (1H, s), 9.85 (1H, s)

Reference Example 5

1-(4-bromophenyl)-3-methoxy-1H-pyrazole-4-carbaldehyde

(step 1)

To a mixture of (4-bromophenyl)hydrazine hydrochloride (50.75 g) in Et_2O (300 mL) and THF (30 mL) was added a 1N aqueous sodium hydroxide solution (270 mL) at 0°C, and the mixture was stirred at room temperature for 1 hr. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated to give orange oil (40.7 g). To a solution of the obtained oil in Et_2O (250 mL) was added dropwise a solution of acetic anhydride (51.5 mL) in Et_2O (50 mL) at 0°C, and the mixture was stirred at 0°C for 30 min. The precipitate was filtrated with Et_2O/hexane to give N'-(4-bromophenyl)acetohydrazide (45.5 g, 67%) as pale-brown crystals.

(step 2)

Using the compound obtained in step 1 and in the same manner as in the method described in Reference Example 4, step 1 - 4, the title compound was obtained.

^{1}H-NMR (300MHz, $CDCl_3$): δ 4.09 (3H, s), 7.55 (2H, d, J=9.0Hz), 7.60 (2H, d, J=9.1Hz), 8.23 (1H, s), 9.86 (1H, s)

Reference Example 6

4-methoxy-2-phenyl-1,3-thiazole-5-carbaldehyde

(step 1)

A solution of benzenecarbothioamide (50 g) and diethyl bromomalonate (95.6 g) in ethanol (350 mL) was refluxed with heating for 2 hrs, and the mixture was cooled to room temperature. The precipitate was filtrated with cold ethanol. The filtrate was concentrated and the precipitate was filtrated with cold ethanol. This operation was done twice to give ethyl 4-hydroxy-2-phenyl-1,3-thiazole-5-carboxylate (79.8 g, 88%) as pale-yellow crystals.

(step 2)

To a solution of the compound obtained in step 1 (17.5 g) and K_2CO_3 (13.6 g) in DMF (200 mL) was added methyl iodide (5.24 mL) at room temperature, and the mixture was stirred at 70°C for 6 hrs. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient;

0→20% ethyl acetate/hexane) and crystallized from ethyl acetate/hexane to give ethyl 4-methoxy-2-phenyl-1,3-thiazole-5-carboxylate (7.32 g, 40%) as white crystals.

(step 3)

To a mixture of the compound obtained in step 2 (5.41 g) in Et_2O (70 mL) and THF (40 mL) was added DIBAL-H (1.5M toluene solution, 54.7 mL) at -78°C, and the mixture was stirred at -78°C for 3 hrs. A saturated aqueous Rochelle salt was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→33% ethyl acetate/hexane) to give (4-methoxy-2-phenyl-1,3-thiazol-5-yl)methanol (4.16 g, 92%) as white crystals.

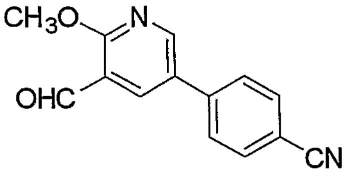
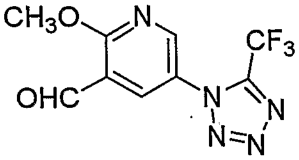
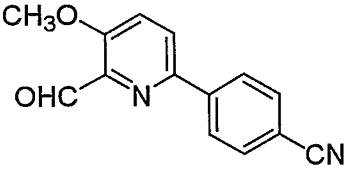
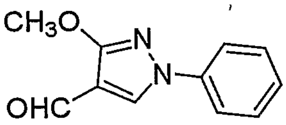
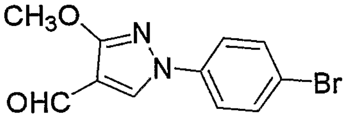
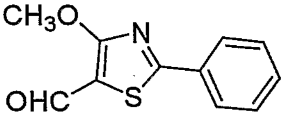
(step 4)

To a solution of the compound obtained in step 3 (1.11 g) in toluene (50 mL) was added manganese dioxide (5.23g), and the mixture was stirred at room temperature for 3 days. The insoluble material was filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 0→20% ethyl acetate/hexane) to give the title compound (0.72 g, 66%) as pale-yellow crystals.

^{1}H-NMR (300MHz, $CDCl_3$): δ 4.25 (3H, s), 7.44-7.53 (3H, m), 7.98-8.02 (2H, m), 9.56 (1H, s)

The compounds described in Reference Examples 1 - 6 are as follows (Table 1).

Table 1

Ref. Ex. No.	structural formula
1	
2	
3	
4	
5	
6	

Reference Example 7

4,6-diisopropoxy-2-isopropylpyrimidine-5-carbaldehyde

(step 1)

To a solution of 4,6-dichloro-2-isopropylpyrimidine (0.96 g) synthesized by a known method (Journal of Medicinal Chemistry (1964), 7(6), 808-11) in methanol (8 mL) was added 1M sodium methoxide/methanol (5 mL) at 0°C, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into an aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent; 10% ethyl acetate/hexane) to give 4-chloro-2-isopropyl-6-methoxypyrimidine (0.80 g, 86%) as colorless oil.

(step 2)

A solution of the compound obtained in step 1 (0.80 g) and sodium hydride (60% in oil, 0.53 g) in 2-propanol (10 mL) was stirred in a stainless tube at 125°C for 2 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous ammonium chloride solution, and then brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent; 10% ethyl acetate/hexane) to give a mixture of 4,6-diisopropoxy-2-isopropylpyrimidine and 4-isopropoxy-2-isopropyl-6-methoxypyrimidine (molar ratio, about 85:15) (0.87 g, 85%) as colorless oil. This was directly used for the next step without further purification.

(step 3)

A solution of the compound obtained in step 2 (0.85 g) and N-bromosuccinimide (0.76 g) in acetic acid (10 mL) was stirred at 50 - 65°C for 2 hrs. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with water and an aqueous sodium hydroxide solution, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent; 10% ethyl acetate/hexane) to give a mixture of 5-bromo-4,6-diisopropoxy-2-

isopropylpyrimidine and 5-bromo-4-isopropoxy-2-isopropyl-6-methoxypyrimidine (molar ratio, about 85:15) (1.02 g, 76%) as colorless oil. This was directly used for the next step without further purification.

(step 4)

To a solution of the compound obtained in step 3 (1.02 g) in THF (20 mL) was added dropwise a 1.6M n-butyllithium-hexane solution (2.4 mL) at -78°C, and the mixture was stirred at -78°C for 1 hr. Ethyl formate (0.65 mL) was added to the reaction mixture, and the mixture was stirred at -78°C for 30 min. To the reaction mixture was added an aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent; 10% ethyl acetate/hexane) to give the title compound (0.46 g, 54%) as colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 1.27 (6H, d, J=6.9Hz), 1.39(12H, d, J=6.3Hz), 2.94 (1H, septet, 6.9Hz), 5.50 (2H, septet, J=6.3Hz), 10.29 (1H, s)

Reference Example 8

4-isopropoxy-2-isopropyl-6-methoxypyrimidine-5-carbaldehyde

(step 1)

To a 1.83M sodium ethoxide/ethanol (200 mL) solution were added dimethyl malonate (19.6 g) and 2-methyl-propionamidine monohydrochloride (15.0 g) at 0°C, and the mixture was heated under reflux for 4 hrs. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water and acidified with 6N hydrochloric acid at 0°C. The precipitate was collected by filtration, and washed with ethanol and diethyl ether to give 2-isopropylpyrimidine-4,6-diol (13.4 g, 71%) as a white powder.

^{1}H-NMR (300MHz, DMSO-d_6): δ 1.17 (6H, d, J=6.9Hz), 2.77 (1H, quintet, 6.9Hz), 5.07 (1H, s), 11.54 (2H, br)

(step 2)

To a 2N aqueous sodium hydroxide solution (17 mL) of the compound obtained in step 1 (5.0g) was added methyl sulfate (3.07 mL) at room temperature. The reaction mixture was heated to 50 - 55°C, and a 2N aqueous sodium hydroxide solution was appropriately added to maintain the reaction mixture at pH 7 - 8.5. The reaction mixture was stirred at 50 - 55°C for 1 hr, and cooled to 0°C. The precipitate was collected by filtration and washed with IPE and ethanol to give 2-isopropyl-6-methoxypyrimidine-4-ol (1.42 g, 26%) as a white powder.

^{1}H-NMR (300MHz, $CDCl_3$): δ 1.33 (6H, d, J=6.9Hz), 2.93 (1H, septet, J=6.9Hz), 3.88 (3H, s), 5.80 (1H, s), 12.94 (1H, brs)

(step 3)

To a solution of the compound obtained in step 2 (5.0 g) in DMF (40 mL) were added cesium fluoride (13.5 g) and isopropyl iodide (15.1g) at room temperature, and the mixture was stirred at 50°C for 2 hrs. The reaction mixture was poured into water, and the resultant product was extracted with ethyl acetate. The organic layer was washed with an aqueous ammonium chloride solution, dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent; 10% ethyl acetate/hexane) to give 4-isopropoxy-2-isopropyl-6-methoxypyrimidine (6.0 g, 96%) as colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 1.28 (6H, d, J=6.9Hz), 1.34

(6H, d, J=6.3Hz), 2.94 (1H, septet, J=6.3Hz), 3.90 (3H, s), 5.27 (1H, septet, J=6.9Hz), 5.78 (1H, s)

(step 4)

To a solution of the compound obtained in step 3 (6.0 g) in acetic acid (40 mL) was added N-bromosuccinimide (6.1 g) at room temperature, and the mixture was stirred at 65°C for 2 hrs. The reaction mixture was concentrated under reduced pressure, and water was added to the residue. The resultant product was extracted with ethyl acetate, and the organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and water. The organic layer was dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent; 10% ethyl acetate/hexane) to give 5-bromo-4-isopropoxy-2-isopropyl-6-methoxypyrimidine (7.3 g, 88%) as colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 1.27 (6H, d, J=6.9Hz), 1.38 (6H, d, J=7.8Hz), 2.95 (1H, septet, J=6.6Hz), 4.01 (3H, s), 5.39 (1H, septet, J=7.8Hz)

(step 5)

A solution of the compound obtained in step 4 (1.0 g) in THF (20 mL) was cooled to -78°C under an argon gas atmosphere. A 1.6M n-butyllithium/hexane solution (2.6 mL) was added, and the mixture was stirred at -78°C for 1 hr. Then, ethyl formate (0.70 mL) was added and the temperature was raised to -30°C. To the reaction mixture was added an aqueous 1M $KHSO_4$ solution. The resultant product was extracted with ethyl acetate, and the organic layer was washed with water and brine. The organic layer was dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent; 10% ethyl acetate/hexane) to give the title compound (0.45 g, 55%) as colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 1.27 (6H, d, J=6.9Hz), 1.39 (6H, d, J=6.3Hz), 2.97 (1H, septet, J=6.9Hz), 4.05 (3H, s), 5.52 (1H, septet, J=6.3Hz), 10.29 (1H, s)

Reference Example 9

1-glycoloylpiperidine-4-carboxylic acid

(step 1)

To a solution of Boc-isonipecotic acid (2.3 g) and DMF (0.05 mL) in THF (15 mL) was added oxalyl chloride (0.95 mL) at 0°C, and the mixture was stirred at 0°C for 1 hr. The reaction mixture was concentrated under reduced pressure at 0 - 10°C, and the residue was dissolved in THF (15 mL). To the THF solution was added a solution of benzyl alcohol (3.13 mL), Et_3N (2.1 mL) and 4-dimethylaminopyridine (0.24 g) in THF (10 mL) at 0°C, and the mixture was stirred at room temperature for 24 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with an aqueous ammonium chloride solution and brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent; 10% ethyl acetate/hexane) to give 4-benzyl 1-tert-butyl piperidine-1,4-dicarboxylate (3.19 g, 100%) as colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 1.43 (9H, s), 1.60-2.00 (4H, m), 2.45-2.55 (1H, m), 2.82 (2H, t like, J=11.4Hz), 3.95-4.05 (2H, m), 5.13 (2H, s), 7.25-7.40 (5H, m)

(step 2)

To a solution of the compound obtained in step 1 (3.19 g) in ethyl acetate (10 mL) was added 4N hydrogen chloride/ethyl acetate (10 mL), and the mixture was stirred at 50°C for 1 hr. The reaction mixture was concentrated under reduced pressure, and the precipitate was filtrated with IPE to give benzyl piperidine-4-carboxylate monohydrochloride (2.53 g, 99%) as a white powder.

^{1}H-NMR (300MHz, DMSO-d_6): δ 2.65 (2H, m), 1.95-2.05 (2H, m), 2.70-2.80 (1H, m), 2.90 (2H, dt, J=12.3, 3.3Hz), 3.22 (2H, dt, J=12.9, 3.9Hz), 5.12 (2H, s), 7.32-7.39 (5H, m), 8.77 (2H, brs)

(step 3)

To a solution of the compound obtained in step 2 (2.50g), Et_3N (1.36 mL) and glycol acid (0.82 g) in acetonitrile (25ml) were added WSC·HCl (2.24 g) and HOBt·H_2O (1.80 g), and the mixture was stirred at room temperature for 12 hrs. The reaction mixture was poured into water and the resultant product was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and brine, dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent gradient; 10→50% ethyl acetate/hexane) to give benzyl 1-glycoloylpiperidine-4-carboxylate (2.71 g, 100%) as colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 1.65-1.80 (2H, m), 1.92-2.10 (2H, m), 2.55-2.70 (1H, m), 2.90-3.10 (2H, m), 3.40-3.55 (1H, dt like), 4.15(2H, s), 4.30-4.40 (1H, m), 5.13 (2H, s), 7.30-7.45 (5H, m), 7.74-7.84 (1H, m)

(step 4)

A solution of the compound obtained in step 3 (6.25 g) and 10% palladium carbon (2.5 g) in ethanol (200 mL) was stirred at room temperature under 1 atm hydrogen atmosphere for 14 hrs. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give the title compound (3.90 g, 93%) as a white powder.

^{1}H-NMR (300MHz, DMSO-d_6): δ 1.30-1.55 (2H, m), 1.75-1.90 (2H, m), 2.44-2.58 (1H, m), 2.77 (1H, t, J=11.7Hz), 3.01 (1H, t, J=11.7Hz), 3.40-4.40 (5H, m), 12.0-12.5

(1H, br)

Reference Example 10

2-cyclopropyl-4-isobutyl-6-methoxypyrimidine-5-carbaldehyde

(step 1)

To a solution of methyl 5-methyl-3-oxohexanoate (14.3 g) synthesized by a known method (WO2006/090915) and cyclopropylcarbamidine monohydrochloride (10.9 g) in ethanol (180 mL) was added sodium ethoxide (18.5 g) at room temperature, and the mixture was heated under reflux for 4 hrs. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water and acidified with 6N hydrochloric acid at 0°C. The resultant product was extracted 3 times with ethyl acetate, and the organic layer was washed with brine. The organic layer was dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent gradient; 50→67% ethyl acetate/hexane) and crystallized from ethyl acetate-IPE to give 2-cyclopropyl-6-isobutylpyrimidine-4-ol (1.31 g, 7.5%) as a white powder.

^{1}H-NMR (300MHz, $CDCl_3$): δ 0.91 (6H, d, J=6.4Hz), 1.03-1.12 (2H, m), 1.14-1.22 (2H, m), 1.86-1.95 (1H, m), 1.99-2.10 (1H, m), 2.31 (2H, d, J=7.2Hz), 6.05 (1H, s), 13.38 (1H, br)

(step 2)

A solution of the compound obtained in step 1 (1.30 g) in phosphorus oxychloride (1.26 mL) was stirred at 110°C for 4 hrs. The reaction mixture was poured into water, and the resultant product was extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium hydrogen carbonate solution, dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent gradient; 1→10% ethyl acetate/hexane) to give 4-chloro-2-cyclopropyl-6-isobutylpyrimidine (1.21 g, 85%) as colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 0.93 (6H, t, J=6.7Hz), 1.03-1.18 (4H, m), 2.05-2.23 (2H, m), 2.52 (2H, d, J=7.2Hz), 6.89 (1H, s)

(step 3)

To a solution of the compound obtained in step 2 (1.20 g) in methanol (14 mL) was added a 28% sodium methoxide/methanol (2 mL) solution at room temperature, and the mixture was heated under reflux for 14 hrs. The reaction mixture was concentrated under reduced pressure, and ice-cold water was poured onto the residue. The resultant product was extracted with ethyl acetate, and the organic layer was washed with water. The organic layer was dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent gradient; 1→10% ethyl acetate/hexane) to give 2-cyclopropyl-4-isobutyl-6-methoxypyrimidine (1.10 g, 93%) as colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 0.91 (6H, d, J=6.4Hz), 0.96-1.00 (2H, m), 1.09-1.14 (2H, m), 2.05-2.16 (2H, m), 2.47 (2H, d, J=7.1Hz), 3.89 (3H, s), 6.26 (1H, s)

(step 4)

To a solution of the compound obtained in step 3 (1.10 g) in acetic acid (12 mL) was added N-bromosuccinimide (1.14 g) at room temperature, and the mixture was stirred at 65°C for 4 hrs. The reaction mixture was concentrated under reduced pressure, and water was added to the residue. The resultant product was extracted with ethyl acetate, and the organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and water. The organic layer was dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent gradient; 1→10% ethyl acetate/hexane) to give 5-bromo-2-cyclopropyl-4-isobutyl-6-methoxypyrimidine (1.43 g, 94%) as colorless oil.

^{1}H-NMR (300MHz, $CDCl_3$): δ 0.96 (6H, d, J=6.8Hz), 0.98-1.05 (2H, m), 1.07-1.12 (2H, m), 2.07-2.28 (2H, m), 2.72 (2H, d, J=7.2Hz), 3.98(3H, s)

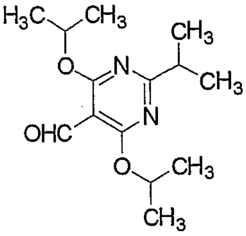
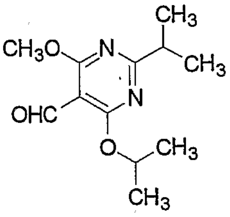
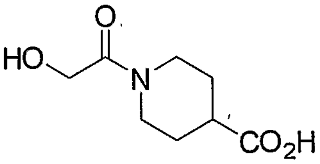
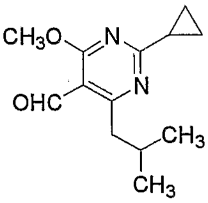
(step 5)

A solution of the compound obtained in step 4 (1.42 g) in THF (25 mL) was cooled to -78°C under an argon gas atmosphere. A 1.6M n-butyllithium/hexane solution (3.74 mL) was added and the mixture was stirred at -78°C for 1 hr. Then, ethyl formate (0.80 mL) was added, and the temperature was raised to -30°C. A 1M aqueous $KHSO_4$ solution was added to the reaction mixture. The resultant product was extracted with ethyl acetate, and the organic layer was washed with water and brine. The organic layer was dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent gradient; 5→25% ethyl acetate/hexane) to give the title compound (0.39 g, 39%) as pale-yellow crystals.

^{1}H-NMR (300MHz, $CDCl_3$): δ 0.91-0.95 (6H, m), 1.06-1.15 (2H, m), 1.20-1.25 (2H, m), 2.08-2.19 (2H, m), 2.96 (2H, d, J=6.8Hz), 4.03 (3H, s), 10.41 (1H, s)

The compounds described in Reference Examples 7 - 10 are as follows (Table 2).

Table 2

Ref. Ex. No.	structural formula
7	
8	
9	
10	

Example 1

N-{2-[(3R,4S)-4-({[5-(4-cyanophenyl)-2-methoxypyridin-3-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide

(step 1)

N-acetylglycine (6.44 g) was suspended in acetonitrile (120 mL). 3-Phenylpiperidin-4-one monohydrochloride (10.58 g), Et_3N (5.06 g) and WSC·HCl (11.50 g) were successively added and the mixture was stirred at 50°C for 2 hrs. The mixture was cooled to 25°C, and partitioned by adding brine/3N hydrochloric acid (1:1) (40 mL). The aqueous layer was re-extracted with acetonitrile (60 mL). The organic layer was combined and washed successively with brine/5N aqueous sodium hydroxide solution (1:1) (40 mL), and twice with brine (40 mL). The organic layer was concentrated under reduced pressure and azeotropically concentrated with ethyl acetate. Ethyl acetate (150 mL) and silica gel (10 g) were added to the residue. The mixture was heated to 70°C and the mixture was stirred for 30 min. Silica gel was filtered off with heating, and washed twice with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure, and azeotropically concentrated with toluene. Toluene (100 mL) was added to the residue and the mixture was dissolved under reflux. The mixture was cooled to 25°C, and the precipitated crystals were collected by filtration and washed twice with toluene (20 mL). The crystals were dried under reduced pressure to give N-[2-oxo-2-(4-oxo-3-phenylpiperidin-1-yl)ethyl]acetamide (8.70 g) as white crystals.

The obtained N-[2-oxo-2-(4-oxo-3-phenylpiperidin-1-yl)ethyl]acetamide (10 g) was suspended in toluene (50 mL). (S)-1-phenylethylamine (6.63 g) and p-toluenesulfonic acid monohydrate (0.35 g) were successively added. The mixture was applied to a Dean-Stark apparatus while refluxing at 110°C for 3 hrs to remove water. The mixture was cooled to 25°C and a sponge nickel catalyst (30 mL), ethanol (50 mL) and Et_3N (3.69 g) were added. A reduction reaction was carried out at 50°C, hydrogen pressure of 0.5-1 MPa until the hydrogen absorption ceased. The reaction mixture was filtered under pressurization under a nitrogen stream, and the sponge nickel catalyst was washed twice with ethanol (10 mL). The filtrate was concentrated under reduced pressure. Water (100 mL) was added to the residue and the mixture was refluxed for 30 min. After cooling to room temperature, a seed crystal was added and the mixture was stirred for 2 hrs. The precipitated crystals were collected by filtration, and washed twice with water (50 mL). Vacuum drying at 60°C for 3 hrs gave N-[2-oxo-2-((3R,4S)-3-phenyl-4-{[(1S)-1-phenylethyl]amino}piperidin-1-yl)ethyl]acetamide (11.64 g) as white crystals.

The obtained N-[2-oxo-2-((3R,4S)-3-phenyl-4-{[(1S)-1-phenylethyl]amino}piperidin-1-yl)ethyl]acetamide (10 g) was dissolved in ethanol (200 mL). 10% Palladium carbon (water-containing product)(5 g) was added. A reduction reaction was carried out at 50°C, hydrogen pressure of 0.5-1 MPa until the hydrogen absorption ceased. The reaction mixture was filtered and palladium carbon was washed twice with ethanol (20 mL). The filtrate was concentrated under reduced pressure to give N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide (7.00 g).

To the obtained N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide (7.00 g) was added ethanol (75 mL), and the mixture was dissolved by refluxing for 30 min. After cooling to 65°C, methanesulfonic acid (2.53 g) was added. After cooling to 25°C, ethyl acetate (150 mL) was added. The precipitation crystals were collected by filtration, and washed twice with ethanol/ethyl acetate (1:3) (40 mL). Drying under reduced pressure gave white crystals (9.07 g). Thereto was added ethanol (75 mL) and the crystals were dissolved by refluxing for 30 min. After cooling to 25°C, the mixture was stirred for 3 hrs and ethyl acetate (150 mL) was added. The precipitated crystals were collected by filtration, and washed twice with ethanol/ethyl acetate (1:3) (40 mL). Drying under reduced pressure gave N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate (8.84 g) as white crystals.

^{1}H-NMR (300MHz, DMSO-d_6): δ 1.83-1.91 (2H, m), 1.88 (3H,s), 2.33 (3H, s), 3.15 (1H, br), 3.58-4.06 (7H, m), 7.30-7.40 (5H, m), 7.78 (3H, br), 7.96-8.03 (1H, m)

MS(FAB): 372(M+H)

elemental analysis value : $C_{16}H_{25}N_3O_5S\cdot1.5H_2O$

Found C, 48.12; H, 7.00; N, 10.59; S, 8.27

Calculated C, 48.23; H, 7.08; N, 10.55; S, 8.05

diastereomer excess: 99.8%de

enantiomer excess: 99.7%ee

(step 2)

To a solution of the compound obtained in step 1 (0.41 g), the compound obtained in Reference Example 1 (0.24 g), and acetic acid (0.2 mL) in methylene chloride (7 mL) was added $NaBH(OAc)_3$ (0.64 g), and the mixture was stirred at room temperature for 12 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution, and then brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (solvent gradient; 50→100% ethyl acetate/hexane) and crystallized from acetone/IPE to give, the title compound (0.33 g, 67%) as white crystals.

MS(ESI+): 498(M+H)

Example 2

tert-butyl (3R,4S)-4-({[5-(4-cyanophenyl)-2-methoxypyridin-3-yl]methyl}amino)-3-phenylpiperidine-1-carboxylate

Using tert-butyl (3R,4S)-4-amino-3-phenylpiperidine-1-carboxylate synthesized by a known method (WO03/101964) and the compound obtained in Reference Example 1, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 499(M+H)

Example 3

4-[6-hydroxy-5-({[(3R,4S)-3-phenylpiperidin-4-yl]amino}methyl)pyridin-3-yl]benzonitrile trihydrochloride

To a mixture of the compound obtained in Example 2 (0.13 g) in methanol (1 mL)-ethyl acetate (2 mL) was added a 4N hydrogen chloride/ethyl acetate (1 mL) solution and the mixture was stirred at 80°C for 10 hrs. The reaction mixture was concentrated to dryness, and crystallized from methanol/IPE to give the title compound (0.080 g, 65%) as white crystals.

MS(ESI+): 385(M-3HCl+H)

Example 4

4-[6-methoxy-5-({[(3R,4S)-3-phenylpiperidin-4-yl]amino}methyl)pyridin-3-yl]benzonitrile tritrifluoroacetate

A solution of the compound obtained in Example 2 (1.8 g) in trifluoroacetic acid (7 mL) was stirred at room temperature for 0.5 hr. The reaction mixture was concentrated to dryness, and crystallized from ethyl acetate/IPE to give the title compound (2.65 g, 100%) as white crystals.

MS(ESI+): 399(M-$3CF_3CO_2H$+H)

Example 5

4-[6-methoxy-5-({[(3R,4S)-3-phenyl-1-(1H-tetrazol-1-ylacetyl)piperidin-4-yl]amino}methyl)pyridin-3-yl]benzonitrile

To a solution of the compound obtained in Example 4 (0.37 g), Et_3N (152m g) and 1H-tetrazol-1-ylacetic acid (0.096 g) in DMF (6 ml) were added WSC·HCl (0.19 g) and HOBt·H_2O (0.12 g), and the mixture was stirred at room temperature for 12 hrs. The reaction mixture was poured into water, and the resultant product was extracted with ethyl acetate. The organic layer washed with a saturated aqueous sodium hydrogen carbonate solution and brine, dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent gradient; 50→100% ethyl acetate/hexane) and crystallized from acetone/IPE to give the title compound (0.20 g, 79%) as white crystals.

MS(ESI+): 509(M+H)

Example 6

4-{5-[({(3R,4S)-1-[(2,6-dioxopiperidin-4-yl)carbonyl]-3-phenylpiperidin-4-yl}amino)methyl]-6-methoxypyridin-3-yl}benzonitrile

Using the compound obtained in Example 4 and 2,6-dioxopiperidine-4-carboxylic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 538(M+H)

Example 7

N-(2-{(3R,4S)-4-[({2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]pyridin-3-yl}methyl)amino]-3-phenylpiperidin-1-yl}-2-oxoethyl)acetamide

Using the compound obtained in Reference Example 2 and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 533(M+H)

Example 8

N-{2-[(3R,4S)-4-({[6-(4-cyanophenyl)-3-methoxypyridin-2-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide

Using the compound obtained in Reference Example 3 and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-

oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 498(M+H)

Example 9

N-[2-((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using 2-cyclopropyl-4-isopropoxy-6-methoxypyrimidine-5-carbaldehyde synthesized by a known method (WO2004/111000) and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 496(M+H)

Example 10

N-{2-[(3R,4S)-4-({[2-cyclopropyl-4-methoxy-6-(2,2,2-trifluoroethoxy)pyrimidin-5-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide

Using 2-cyclopropyl-4-methoxy-6-(2,2,2-trifluoroethoxy)pyrimidine-5-carbaldehyde synthesized by a known method (WO2003/053957) and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 536(M+H)

Example 11

tert-butyl (3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidine-1-carboxylate

Using 2-cyclopropyl-4-isopropoxy-6-methoxypyrimidine-5-carbaldehyde synthesized by a known method (WO2004/111000) and tert-butyl (3R,4S)-4-amino-

3-phenylpiperidine-1-carboxylate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 497(M+H)

Example 12

(3R,4S)-N-[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]-3-phenylpiperidine-4-amine ditrifluoroacetate

To a solution of the compound obtained in Example 11 (0.40 g) in methylene chloride (4 mL) was added trifluoroacetic acid (4 mL), and the mixture was stirred at room temperature for 4 hrs. The reaction mixture was concentrated, ethanol was added and excess trifluoroacetic acid was evaporated to give the title compound (0.50 g, 100%) as colorless oil.

MS(ESI+): 397(M-2CF_3CO_2H+H)

Example 13

(3R)-3-(acetylamino)-4-((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-4-oxobutanamide

Using the compound obtained in Example 12 and N^2-acetyl-D-aspartic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 553(M+H)

Example 14

5-[2-((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

Using the compound obtained in Example 12 and (5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 522(M+H)

Example 15

2-((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethanol

Using the compound obtained in Example 12 and hydroxyacetic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 455(M+H)

Example 16

1-[((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)carbonyl]cyclopropanecarboxamide

Using the compound obtained in Example 12 and 1-(aminocarbonyl)cyclopropanecarboxylic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 508(M+H)

Example 17

(3R,4S)-N-[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]-1-[(1-methyl-1H-imidazol-5-yl)carbonyl]-3-phenylpiperidine-4-amine

Using the compound obtained in Example 12 and 1-methyl-1H-imidazole-5-carboxylic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 505(M+H)

Example 18

4-[((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)carbonyl]piperidine-2,6-dione

Using the compound obtained in Example 12 and 2,6-dioxopiperidine-4-carboxylic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 536(M+H)

Example 19

(3R,4S)-N-[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]-3-phenyl-1-(pyridin-3-ylcarbonyl)piperidine-4-amine

Using the compound obtained in Example 12 and nicotinic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 502(M+H)

Example 20

(3R,4S)-N-[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]-1-[(methylsulfonyl)acetyl]-3-phenylpiperidine-4-amine

Using the compound obtained in Example 12 and methanesulfonylacetic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 517(M+H)

Example 21

N-[2-((3R,4S)-4-{[(2-cyclopropyl-4,6-diisopropoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using 2-cyclopropyl-4,6-diisopropoxypyrimidine-5-carbaldehyde synthesized by a known method (WO2004/111000) and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 524(M+H)

Example 22

N-[2-((3R,4S)-4-{[(3-methoxy-1-phenyl-1H-pyrazol-4-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using the compound obtained in Reference Example 4 and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-

oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 462(M+H)

Example 23

N-{2-[(3R,4S)-4-({[1-(4-bromophenyl)-3-methoxy-1H-pyrazol-4-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide

Using the compound obtained in Reference Example 5 and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 540, 542(M+H)

Example 24

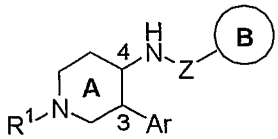
N-[2-((3R,4S)-4-{[(4-methoxy-2-phenyl-1,3-thiazol-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using the compound obtained in Reference Example 6 and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 479(M+H)

The compounds described in Reference Examples 1 - 24 are as follows (Tables 3 - 5).

Table 3



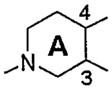
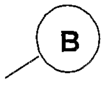
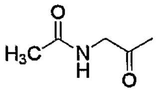
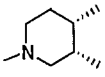
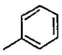
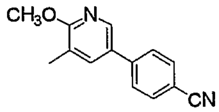
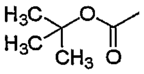
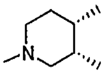
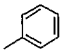
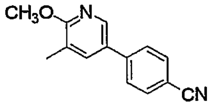
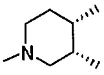
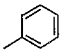
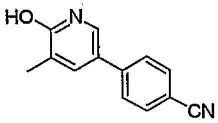
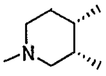
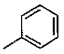
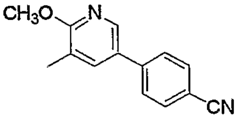
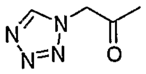
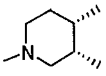
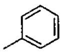
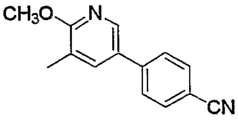
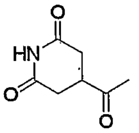
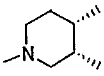
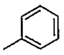
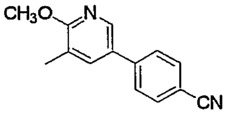
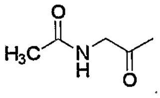
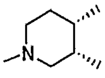
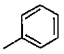
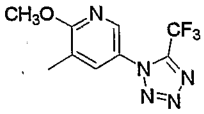
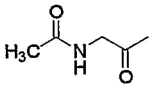
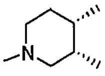
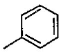
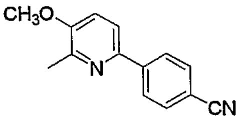
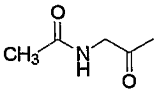
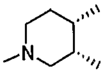
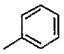
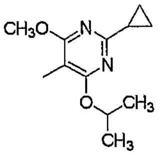
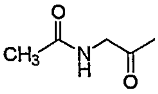
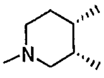
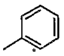
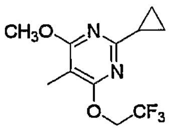
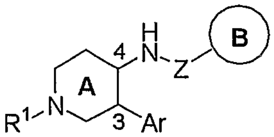
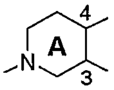
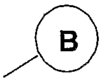
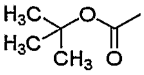
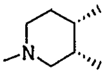
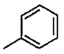
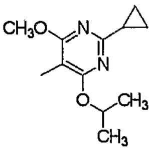
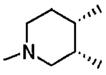
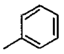
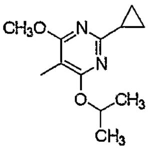
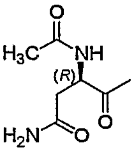
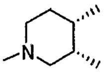
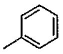
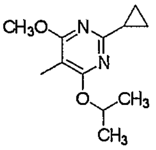
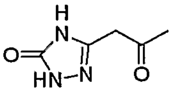
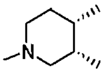
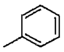
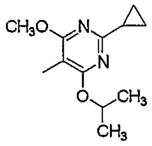
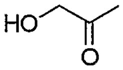
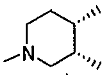
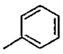
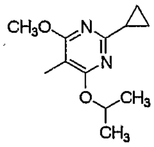
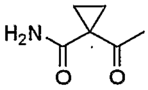
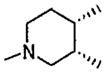
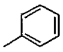
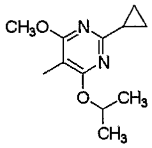
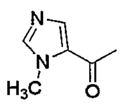
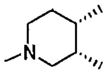
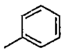
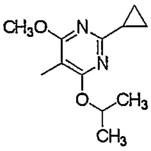
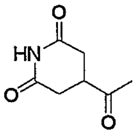
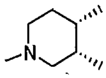
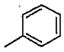
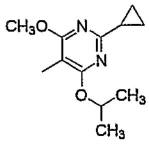
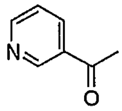
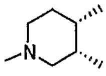
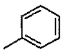
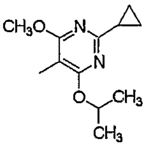
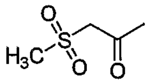
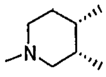
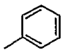
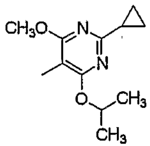
Ex. No.	R^1		Ar	Z		additive	MS (ESI)
1		 (3R,4S)		CH_2			498
2		 (3R,4S)		CH_2			499
3	H	 (3R,4S)		CH_2		$3HCl$	385
4	H	 (3R,4S)		CH_2		$3CF_3CO_2H$	399
5		 (3R,4S)		CH_2			509
6		 (3R,4S)		CH_2			538
7		 (3R,4S)		CH_2			533
8		 (3R,4S)		CH_2			498
9		 (3R,4S)		CH_2			496
10		 (3R,4S)		CH_2			536

Table 4



Ex. No.	R^1		Ar	Z		additive	MS (ESI)
11		 (3*R*,4*S*)		CH_2			497
12	H	 (3*R*,4*S*)		CH_2		$2CF_3CO_2H$	397
13		 (3*R*,4*S*)		CH_2			553
14		 (3*R*,4*S*)		CH_2			522
15		 (3*R*,4*S*)		CH_2			455
16		 (3*R*,4*S*)		CH_2			508
17		 (3*R*,4*S*)		CH_2			505
18		 (3*R*,4*S*)		CH_2			536
19		 (3*R*,4*S*)		CH_2			502
20		 (3*R*,4*S*)		CH_2			517

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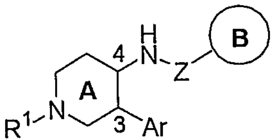
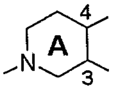
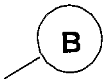
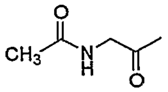
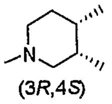
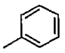
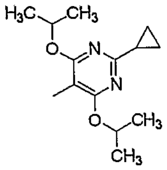
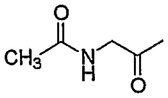
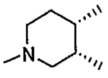
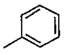
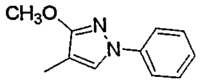
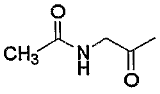
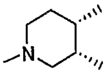
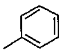
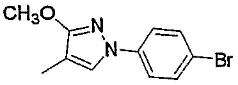
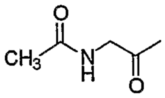
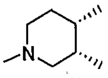
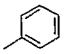
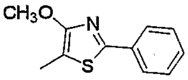


Ex. No.	R^1		Ar	Z		additive	MS (ESI)
21		 (3R,4S)		CH_2			524
22		 (3R,4S)		CH_2			462
23		 (3R,4S)		CH_2			540, 542
24		 (3R,4S)		CH_2			479

Example 25

N-[2-((3R,4S)-4-{[(4,6-diisopropoxy-2-isopropylpyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using the compound obtained in Reference Example 7 and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 526(M+H)

Example 26

(3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-N-ethyl-3-phenylpiperidine-1-carboxamide

To a solution of the compound obtained in Example 12 and Et_3N (0.23 mL) in THF (5 mL) was added ethyl isocyanate (0.033 mL) at 0°C, and the mixture was stirred at room temperature for 3 days. The reaction mixture was poured into water, and the resultant product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (solvent gradient; 0→3% methanol/ethyl acetate) and crystallized from acetone/IPE to give the title compound (0.055 g, 51%) as white crystals.

MS(ESI+): 468(M+H)

Example 27

4-[5-({[(3R,4S)-1-(3-hydroxy-3-methylbutanoyl)-3-phenylpiperidin-4-yl]amino}methyl)-6-methoxypyridin-3-yl]benzonitrile

Using the compound obtained in Example 4 and β-hydroxyisovaleric acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 499(M+H)

Example 28

4-{6-methoxy-5-[({(3R,4S)-1-[(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-3-phenylpiperidin-4-yl}amino)methyl]pyridin-3-yl}benzonitrile

Using the compound obtained in Example 4 and (5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 524(M+H)

Example 29

2-{4-[((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)carbonyl]piperidin-1-yl}-2-oxoethanol

Using the compound obtained in Example 12 and the compound obtained in Reference Example 9, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 566(M+H)

Example 30

N-[2-((3R,4S)-4-{[(4-isopropoxy-2-isopropyl-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using the compound obtained in Reference Example 8 and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 498(M+H)

Example 31

N-[2-((3R,4S)-4-{[(5-bromo-2-methoxy-4,6-dimethylpyridin-3-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using 5-bromo-2-methoxy-4,6-dimethylnicotinaldehyde synthesized by a known method (Journal of Organic Chemistry (2003), 68(9), 3446-3453) and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 503, 505(M+H)

Example 32

N-[2-((3R,4S)-4-{[(2-cyclopropyl-4,6-dimethoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using 2-cyclopropyl-4,6-dimethoxypyrimidine-5-carbaldehyde synthesized by a known method (WO 2003/053957) and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 468(M+H)

Example 33

1-[2-((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]pyrrolidine-2,5-dione

Using the compound obtained in Example 12 and (2,5-dioxopyrrolidin-1-yl)acetic acid, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+):536(M+H)

Example 34

1-[2-((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]pyrimidine-2,4(1H,3H)-dione

Using the compound obtained in Example 12 and (2,4-dioxo-3,4-dihydropyrimidine-1(2H)-yl)acetic acid synthesized by a known method (Journal of Organic Chemistry (2004), 69(24), 8183-8185), and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+):536(M+H)

Example 35

6-[((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)carbonyl]pyrimidine-2,4(1H,3H)-dione

Using the compound obtained in Example 12 and 2,4-dihydroxypyrimidine-5-carboxylic acid monohydrate, and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+):535(M+H)

Example 36

N-[2-((3R,4S)-4-{[(2-ethoxy-4,6-dimethoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using 2-ethoxy-4,6-dimethoxypyrimidine-5-carbaldehyde synthesized by a known method (WO2003/053957) and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 472(M+H)

Example 37

N-[2-((3R,4S)-4-{[(2-cyclopropyl-4-isobutyl-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide

Using the compound obtained in Reference Example 10 and N-{2-[(3R,4S)-4-amino-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide methanesulfonate, and in the same manner as in the method described in Example 1, step 2, the title compound was obtained.

MS(ESI+): 494(M+H)

Example 38

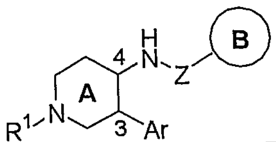
4-{5-[({(3R,4S)-1-[(5,5-dimethyl-2,4-dioxo-1,3-oxazolidin-3-yl)acetyl]-3-phenylpiperidin-4-yl}amino)methyl]-6-methoxypyridin-3-yl}benzonitrile

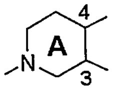
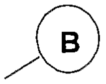
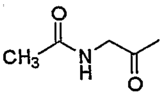
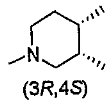
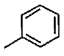
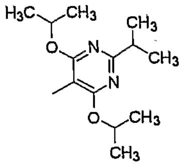
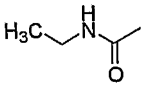
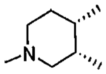
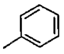
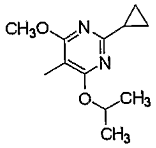
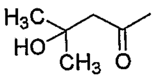
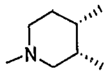
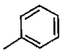
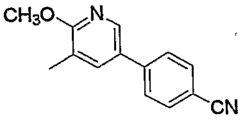
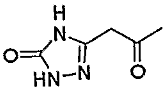
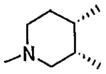
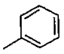
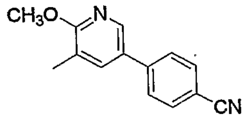
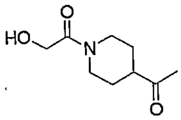
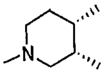
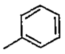
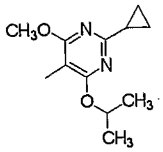
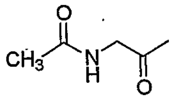
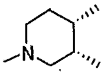
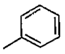
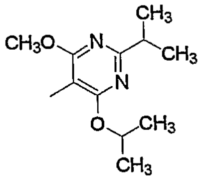
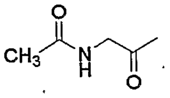
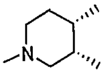
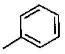
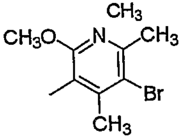
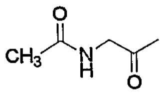
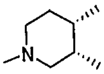
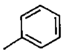
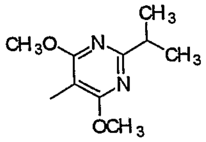
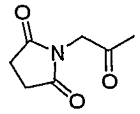
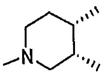
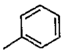
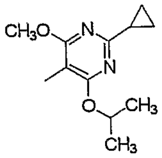
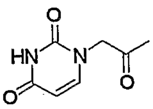
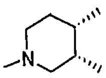
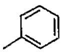
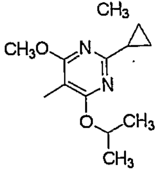
Using the compound obtained in Example 4 and (5,5-dimethyl-2,4-dioxo-1,3-oxazolidin-3-yl)acetic acid synthesized by a known method (Journal of the American Chemical Society (1948), 70, 1021-1022), and in the same manner as in the method described in Example 5, the title compound was obtained.

MS(ESI+): 568(M+H)

The compounds described in Reference Examples 25 - 38 are as follows (Tables 6 - 7).

Table 6



Ex. No.	R^1		Ar	Z		additive	MS (ESI)
25		 (3R,4S)		CH_2			526
26		 (3R,4S)		CH_2			468
27		 (3R,4S)		CH_2			499
28		 (3R,4S)		CH_2			524
29		 (3R,4S)		CH_2			566
30		 (3R,4S)		CH_2			498
31		 (3R,4S)		CH_2			503, 505
32		 (3R,4S)		CH_2			468
33		 (3R,4S)		CH_2			536
34		 (3R,4S)		CH_2			549

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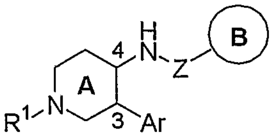
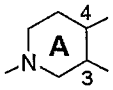
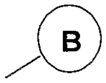
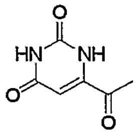
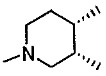
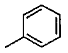
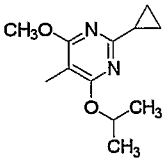
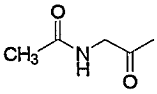
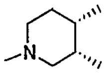
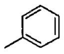
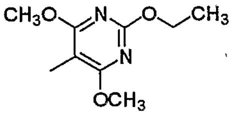
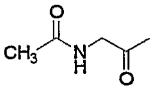
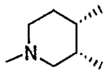
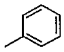
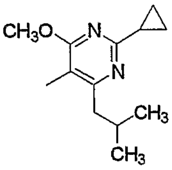
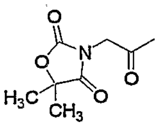
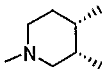
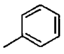
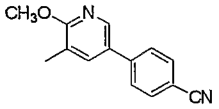


Ex. No.	R^1		Ar	Z		additive	MS (ESI)
35		 (3*R*,4*S*)		CH_2			535
36		 (3*R*,4*S*)		CH_2			472
37		 (3*R*,4*S*)		CH_2			494
38		 (3*R*,4*S*)		CH_2			568

Preparative Example 1

(1)	Compound of Example 1	10 mg
(2)	Lactose	60 mg
(3)	Corn starch	35 mg
(4)	Hydroxypropylmethylcellulose	3 mg
(5)	Magnesium stearate	2 mg

A mixture of 10 mg of the compound obtained in Example 1, 60 mg of lactose and 35 mg of corn starch is granulated using 0.03 mL of an aqueous solution of 10 wt% hydroxypropylmethylcellulose (3 mg as hydroxypropylmethylcellulose), and then dried at 40°C and sieved. The obtained granules are mixed with 2 mg of magnesium stearate and compressed. The obtained uncoated tablets are sugar-coated with an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic. The thus-coated tablets are glazed with bees wax to obtain finally-coated tablets.

Preparative Example 2

(1) Compound of Example 1	10 mg
(2) Lactose	70 mg
(3) Corn starch	50 mg
(4) Soluble starch	7 mg
(5) Magnesium stearate	3 mg

10 mg of the compound obtained in Example 1 and 3 mg of magnesium stearate are granulated with 0.07 mL (7 mg as soluble starch) of an aqueous soluble starch solution, dried, and mixed with 70 mg of lactose and 50 mg of corn starch. The mixture is compressed to obtain tablets.

Reference Preparative Example 1

(1) Rofecoxib	5.0 mg
(2) Table salt	20.0 mg
(3) Distilled water	to 2 mL of total volume

5.0 mg of rofecoxib and 20.0 mg of table salt are dissolved in distilled water, and water is added to make 2.0 mL of total volume. The solution is filtered, and filled into 2 mL of ampoule under sterile condition. The ampoule is sterilized, and then sealed to obtain a solution for injection.

Reference Preparative Example 2

(1) Rofecoxib	50 mg
(2) Lactose	34 mg
(3) Corn starch	10.6 mg
(4) Corn starch (paste)	5 mg
(5) Magnesium stearate	0.4 mg
(6) Calcium carboxymethylcellulose	20 mg
total	120 mg

The above-mentioned (1) to (6) are mixed according to a conventional method and were tableted by a tablet machine to obtain tablets.

Preparative Example 3

The formulation prepared in Preparative Example 1 or 2, and the formulation prepared in Reference Preparative Example 1 or 2 are combined.

Experimental Example 1

Radioligand receptor binding inhibitory activity (Binding inhibitory activity using receptor from human lymphoblast cells (IM-9))

The method of M. A. Cascieri et al., "Molecular Pharmacology 42, p. 458 (1992)" was modified and used. The receptor was prepared from human lymphoblast cells (IM-9).

IM-9 cells (2×10^5 cells/ mL) were incubated for 3 days, which was then subjected to centrifuge for 10 min at 500 × G to obtain cell pellets. The obtained pellets were washed with PBS (GIBCO), which were then homogenized using Polytron homogenizer ("Kinematika", Germany) in Buffer A (50 mM Tris-HCl buffer (pH 7.4) containing 120 mM sodium chloride, 5 mM potassium chloride, 2 μg/mL chymostatin, 40 μg/mL bacitracin, 40 μg/mL APMSF and 1 mM ethylenediamine tetraacetate), which was subjected to centrifugation at 100,000 × G for 40 min. The sediment fraction was suspended in Buffer B (50 mM Tris-HCl (pH 7.4), 0.02% bovine serum albumin, 2 μg/mL chymostatin, 40 μg/mL bacitracin, 40 μg/mL (p-amidinophenyl)methanesulfonyl fluoride (APMSF), 3 mM $MgCl_2$), which was then preserved frozen (-80°C) as a specimen of the receptor.

Buffer B (50 μL) was added to a 96 well microassay plate (Corning). Thereto was added the membrane standard (50 μL) suspended in buffer B at 250 μg/mL. A measurement buffer (50 μL) containing 2% dimethyl sulfoxide was added to examine the total binding, 50 μL of 4 μM non-labeled SP diluted with a measurement buffer containing 2% dimethyl sulfoxide was added to examine the nonspecific binding, and 50 µL of a test compound (containing 2% dimethyl sulfoxide) diluted with a measurement buffer was added to examine the binding inhibitory activity of the test compound. Furthermore, 400 µM of a ^{125}I-Bolton Hunter substance P (^{125}I-BHSP) solution (50 µL) was added to each well.

After the reaction at 25°C for 30 min, using a cell harvester (Perkin-Elmer), rapid filtration was carried out through GF/C filter plate (Perkin-Elmer) to stop the reaction and then GF/C filter plate was washed ten times with 250 µl of 50 mM Tris-HCl buffer (pH 7.4) containing 0.02% bovine serum albumin. The GF/C filter plate was dried, microscinti-0 (20 µL) was added and the radioactivity was measured by TopCount (Perkin-Elmer). The GF/C filter plate had been immersed in 0.3% polyethylene imine for 24 hrs before use.

The specific binding is a value obtained by subtracting nonspecific binding from the total binding. The binding inhibitory activity of the test compound is shown by a ratio of a value obtained by subtracting the measurement value when the test compound was added from the total binding, to the specific binding.

The antagonistic activity of each compound obtained in Examples was determined in terms of the concentration necessary to cause 50% inhibition (IC_{50} value) under the above-described conditions, and the results were shown in Table 8.

Table 8

Ex. No.	IC_{50} (nM)
1	0.015
7	0.075
9	0.021
23	0.019

The radio ligand means substance P labeled with

[^{125}I].

From the Table, it has been clarified that the compounds of the present invention have superior antagonistic action for the substance P receptor.

Industrial Applicability

Compound (I), a salt thereof and a prodrug of the present invention have a high tachykinin receptor antagonistic action, particularly a substance P receptor antagonistic action, are rich in sustainability, show small toxicity, are safe as pharmaceutical agents, and show a small influence on other agents. Therefore, the compound (I) a salt thereof and a prodrug thereof of the present invention are useful as pharmaceutical agents, such as tachykinin receptor antagonists, agents for the prophylaxis or treatment of lower urinary tract diseases and the like.

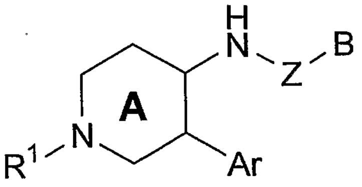
This application is based on Provisional Patent Application No. 60/763,894 filed in U.S.A., the contents of which are hereby incorporated by reference.

All patents, patent publications and other publications identified or referenced herein are incorporated in full herein by this reference in their entireties.

Although only some exemplary embodiments of this invention have been described in detail above, those skilled in the art will readily appreciated that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention.

CLAIMS

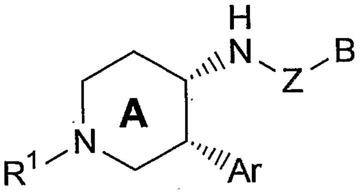
1. A compound represented by the formula (I):



(I)

wherein
Ar is a phenyl group optionally having substituent(s),
R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),
Z is a methylene group optionally having C_{1-6} alkyl group(s),
ring A is a piperidine ring optionally further having substituent(s), and
B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring)· or a salt thereof.

2. The compound of claim 1, which is an optically active form represented by the formula (I-a)



(I-a)

wherein each symbol is as defined in claim 1.

3. The compound of claim 1, wherein Ar is a phenyl group.

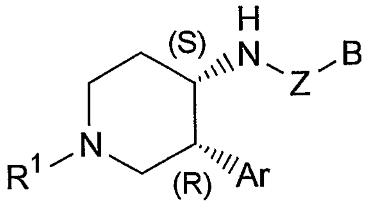
4. The compound of claim 1, wherein R^1 is a hydrogen atom or an acyl group.

5. The compound of claim 1, wherein R^1 is
(1) a hydrogen atom,
(2) a C_{1-6} alkyl-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl-carbonylamino group, (b) a 5- or 6-membered nitrogen-containing heterocyclic group optionally having 1 to 4 substituents selected from the group consisting of a C_{1-6} alkyl group and an oxo group, (c) a carbamoyl group, (d) a hydroxy group and (e) a C_{1-6} alkylsulfonyl group,
(3) a C_{1-6} alkoxy-carbonyl group,
(4) a C_{3-6} cycloalkyl-carbonyl group optionally having carbamoyl group(s),
(5) a 5- or 6-membered nitrogen-containing heterocycle-carbonyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) an oxo group and (c) C_{1-6} alkyl-carbonyl group optionally having hydroxy group(s), or
(6) a mono-C_{1-6} alkyl-carbamoyl group.

6. The compound of claim 1, wherein Z is a methylene group.

7. The compound of claim 1, wherein ring A is a piperidine ring without further substituent(s).

8. The compound of claim 1, which is an optically active form represented by the formula (I-b)



(I-b)

wherein each symbol is as defined in claim 1.

9. The compound of claim 1, wherein B is a nitrogen-

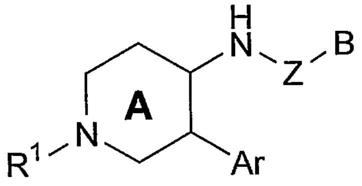
containing aromatic heterocyclic group optionally having substituent(s).

10. The compound of claim 1, wherein B is (1) a pyridyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a halogen atom, (b) a C_{1-6} alkyl group, (c) a hydroxy group, (d) a C_{1-6} alkoxy group, (e) a C_{6-10} aryl group optionally having cyano group(s) and (f) a nitrogen-containing aromatic heterocyclic group optionally substituted by C_{1-6} alkyl group(s) optionally having halogen atom(s),
(2) a pyrimidyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkyl group, (b) a C_{1-6} alkoxy group optionally having halogen atom(s) and (c) a C_{3-6} cycloalkyl group,
(3) a pyrazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group optionally having halogen atom(s) or
(4) a thiazolyl group optionally having 1 to 3 substituents selected from the group consisting of (a) a C_{1-6} alkoxy group and (b) a C_{6-10} aryl group.

11. N-{2-[(3R,4S)-4-({[5-(4-Cyanophenyl)-2-methoxypyridin-3-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide,
N-(2-{(3R,4S)-4-[({2-methoxy-5-[5-(trifluoromethyl)-1H-tetrazol-1-yl]pyridin-3-yl}methyl)amino]-3-phenylpiperidin-1-yl}-2-oxoethyl)acetamide,
N-[2-((3R,4S)-4-{[(2-cyclopropyl-4-isopropoxy-6-methoxypyrimidin-5-yl)methyl]amino}-3-phenylpiperidin-1-yl)-2-oxoethyl]acetamide, or
N-{2-[(3R,4S)-4-({[1-(4-bromophenyl)-3-methoxy-1H-pyrazol-4-yl]methyl}amino)-3-phenylpiperidin-1-yl]-2-oxoethyl}acetamide,

or a salt thereof.

12. A prodrug of a compound represented by the formula (I):



(I)

wherein

Ar is a phenyl group optionally having substituent(s),

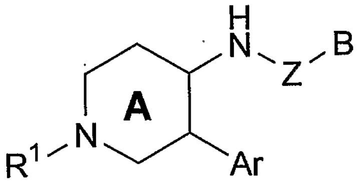
R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),

Z is a methylene group optionally having C_{1-6} alkyl group(s),

ring A is a piperidine ring optionally further having substituent(s), and

B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring) or a salt thereof.

13. A pharmaceutical composition comprising a compound represented by the formula (I):



(I)

wherein

Ar is a phenyl group optionally having substituent(s),

R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),

Z is a methylene group optionally having C_{1-6} alkyl group(s), ring A is a piperidine ring optionally further having substituent(s), and

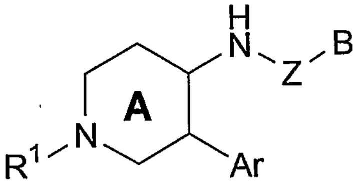
B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring) or a salt thereof, or a prodrug thereof and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13, which is a tachykinin receptor antagonist.

15. The pharmaceutical composition of claim 13, which is an agent for the prophylaxis or treatment of lower urinary tract disease, gastrointestinal disease or central nervous system disease.

16. The pharmaceutical composition of claim 13, which is an agent for the prophylaxis or treatment of overactive bladder, irritable bowel syndrome, inflammatory bowel disease, vomiting, nausea, depression, anxiety neurosis, anxiety, pelvic visceral pain or interstitial cystitis.

17. A method for the prophylaxis or treatment of lower urinary tract disease, gastrointestinal disease or central nervous system disease in a mammal, which comprises administering an effective amount of a compound represented by the formula (I):



(I)

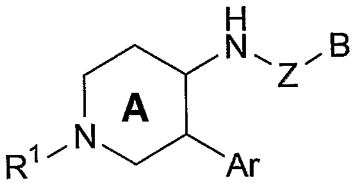
wherein

Ar is a phenyl group optionally having substituent(s),

R^1 is a hydrogen atom, a hydrocarbon group optionally

having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),
Z is a methylene group optionally having C_{1-6} alkyl group(s),
ring A is a piperidine ring optionally further having substituent(s), and
B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring) or a salt thereof, or a prodrug thereof.

18. Use of a compound represented by the formula (I):



(I)

wherein
Ar is a phenyl group optionally having substituent(s),
R^1 is a hydrogen atom, a hydrocarbon group optionally having substituent(s), an acyl group or a heterocyclic group optionally having substituent(s),
Z is a methylene group optionally having C_{1-6} alkyl group(s),
ring A is a piperidine ring optionally further having substituent(s), and
B is a monocyclic aromatic heterocyclic group optionally having substituent(s) (substituents of monocyclic aromatic heterocycle may be bonded to each other to form a ring) or a salt thereof, or a prodrug thereof for the production of an agent for the prophylaxis or treatment of lower urinary tract disease, gastrointestinal disease or central nervous system disease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2007/052160

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 C07D401/14 C07D417/12 A61K31/435 A61P13/00
A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/101964 A (TAKEDA CHEMICAL INDUSTRIES LTD [JP]; IKEURA YOSHINORI [JP]; HASHIMOTO) 11 December 2003 (2003-12-11) Claim 1 in combination with the definition of "B" in paragraphs [0009] and [0073] of the description examples 23,24,71-78 -----	1-18
A	US 6 297 259 B1 (MAYNARD GEORGE P [US] ET AL) 2 October 2001 (2001-10-02) the whole document -----	1-18
A	US 2002/002164 A1 (DORN CONRAD P [US] ET AL) 3 January 2002 (2002-01-03) the whole document -----	1-18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search 23 April 2007	Date of mailing of the international search report 04/05/2007
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Fritz, Martin

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2007/052160

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

Although claims 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2007/052160

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03101964 A	11-12-2003	AU 2003241903 A1	19-12-2003
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US 6297259 B1	02-10-2001	NONE	
US 2002002164 A1	03-01-2002	NONE	