DESCRIPTION

2-ARYL-8-OXODIHYDROPURINE DERIVATIVE, PROCESS FOR THE PREPARATION THEREOF, PHARMACEUTICAL COMPOSITION CONTAINING THE SAME, AND INTERMEDIATE THEREFOR

TECHNICAL FIELD

The present invention relates to a novel 2-aryl-8-oxodihydropurine derivative selectively acting on the peripheral-type benzodiazepine receptors, more particularly, a 2-aryl-8-oxodihydropurine derivative having an acetamide moiety at the 7-position or the 9-position of the purine nucleus, a process for the preparation thereof, a pharmaceutical composition containing the same, and an intermediate therefor.

BACKGROUND ART

In the tissues of the mammals including human, there are three kinds of benzodiazepine (hereinafter, occasionally referred to as BZ) recognition sites, and each is named as central-type (ω_1, ω_2) benzodiazepine receptors and a peripheral-type (ω_3) benzodiazepine receptor, respectively (hereinafter, occasionally referred to as BZω_1-receptor, BZω_2-receptor and BZω_3-receptor, respectively). Among them, the central-type BZ-receptors are the binding sites for BZ-compounds, and are present on the γ-aminobutyric acid (hereinafter, occasionally referred to as "GABA")$_A$-BZ-receptor-Cl^- ion channel complexes. On the other hand, the peripheral-type BZ-receptor widely distributes in the central or peripheral tissues or organs such as brain,

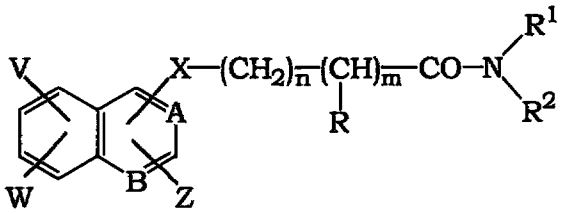
kidney, liver, heart, etc., and it especially distributes with high density in the cells of the endocrinium organs such as adrenal glands, testicles, etc., or in the cells deeply participating in the inflammation-immune system in whole body such as mast cells, lymphocytes, macrophages, blood platelets, etc., so that the physiological roles of the peripheral-type BZ-receptor have recently been drawing attention. On the other hand, the peripheral-type BZ-receptor is present a lot in the mitochondrial membrane of glial cells in the brain, and it participates in cholesterol influx into the mitochondrial membrane, and hence, it is thought to act on the biosynthesis pathway of cholesterol into neurosteroids such as progesterone, allopregnanolone, etc., via pregnenolone. Thus, it is considered that stimulation of the peripheral-type BZ-receptor accelerates the synthesis of neurosteroids in the brain which affect the chloride ion channel gating process by binding to the neurosteroid-specific recognition site (which is a different site from the benzodiazepine receptor) on the $GABA_A$-BZ receptor-Cl^- ion channel complexes [cf. Romeo, E., et al., J. Pharmacol. Exp. Ther., **262**, 971-978 (1992)].

A compound having a non-BZ nucleus and selectively showing an affinity for the peripheral-type BZ-receptor has been disclosed in Japanese Patent First Publication (Kokai) No. 201756/1983 (= EP-A-94271), and since then, various compounds have been disclosed in many patent publications, etc., however, there is no compound which has actually been used as a medicament.

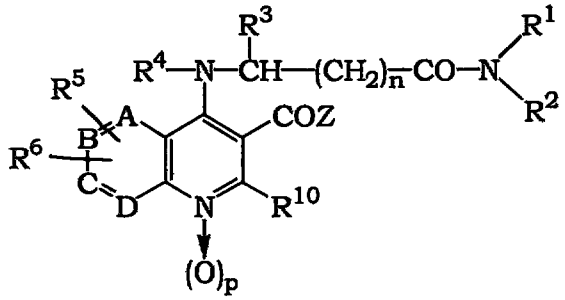
As a compound having a non-BZ nucleus and selectively showing an affinity for the peripheral-type BZ-receptors, the following

compounds have been known.

Japanese Patent First Publication (Kokai) No. 5946/1987 (= USP 4788199, EP-A-205375 (patent family)) discloses that amide compounds of the following formula are bound to the peripheral-type BZ-receptor, and are useful as anxiolytics, anticonvulsants and drugs for treatment of angina pectoris, and in the treatment of immuno-deficiency syndrome.

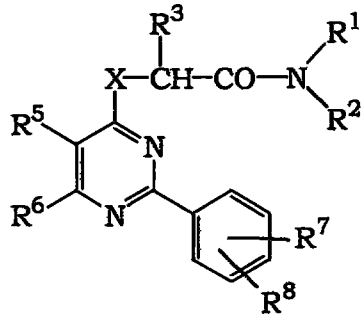


Japanese Patent First Publication (Kokai) No. 32058/1990 (= EP-A-346208, USP 5026711) discloses that 4-amino-3-carboxyquinoline compounds of the following formula show an affinity for the peripheral-type BZ-receptor both *in vitro* and *in vivo*, and can be used in the prophylaxis or treatment of human cardiovascular diseases, or as an antiallergic agent, or in the prophylaxis or treatment of infectious diseases, or in the treatment of anxiety.



WO 96-32383 publication discloses that the acetamide derivative of the following formula selectively acts on BZ_{ω_3}-receptor, and

has anxiolytic activity and anti-rheumatoid activity so that it can be used in the treatment of anxiety-relating diseases or immune diseases.



wherein X is -O- or -NR^4-; R^1 is a hydrogen atom, a lower alkyl group, a lower alkenyl group, or a cycloalkyl-lower alkyl group; R^2 is a lower alkyl group, a cycloalkyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted phenyl-lower alkyl group, etc.; R^3 is a hydrogen atom, a lower alkyl group, or a hydroxy-lower alkyl group; R^4 is a hydrogen atom, a lower alkyl group, etc.; R^5 is a hydrogen atom, a lower alkyl group, a lower alkenyl group, a hydroxy-lower alkyl group, a substituted or unsubstituted benzyloxy-lower alkyl group, an acyloxy-lower alkyl group, a lower alkoxy-lower alkyl group, an amino group, a mono- or di-lower alkylamino group, an acylamino group, an amino-lower alkyl group, a nitro group, a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, a carboxyl group, a protected carboxyl group, a carboxy-lower alkyl group, or a protected carboxy-lower alkyl group; R^6 is a hydrogen atom, a lower alkyl group, a trifluoromethyl group, or a substituted or unsubstituted phenyl group, or R^5 and R^6 may optionally combine to form -$(CH_2)_n$- (n is 3, 4, 5 or 6); R^7 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy group, an amino group, a

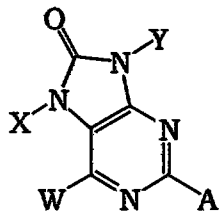
mono- or di-lower alkylamino group, a cyano group, or a nitro group; and R^8 is a hydrogen atom, a halogen atom, a lower alkyl group, or a lower alkoxy group.

DISCLOSURE OF INVENTION

The present inventors have intensively studied in order to prepare a compound acting selectively and potently on $BZ\omega_3$-receptor, and have found the 2-aryl-8-oxodihydropurine derivatives of the following formula (I), and finally have accomplished the present invention.

An object of the present invention is to provide a novel 2-aryl-8-oxodihydropurine derivative acting selectively and potently on $BZ\omega_3$-receptor, more particularly, to provide a 2-aryl-8-oxodihydropurine derivative having an acetamide moiety on the 7-position or the 9-position of the purine nucleus. Especially, the present invention provides a useful compound having an anti-anxiety activity. Another object of the present invention is to provide a process for preparing said compound. Still further object of the present invention is to provide a pharmaceutical composition containing said compound. Further object of the present invention is to provide an intermediate for preparing said compound. These and other objects and advantages of the present invention are obvious to any person skilled in the art from the following disclosure.

The present invention provides a 2-aryl-8-oxodihydropurine derivative of the following formula (I), a pharmaceutically acceptable acid addition salt thereof, a process for the same, and a pharmaceutical composition containing the same:



(I)

wherein W is a hydrogen atom, a lower alkyl group, a halogen atom, a lower alkoxy group, an amino group, a mono- or di-lower alkylamino group, or a substituted or unsubstituted phenyl group;

X is a hydrogen atom, a lower alkyl group, a cycloalkyl-lower alkyl group, a substituted or unsubstituted phenyl-lower alkyl group, a lower alkenyl group, a carbamoyl group, a di-lower alkylcarbamoyl group, or a group of the formula (Q):

$$-CH(R^3)CON(R^1)(R^2) \qquad (Q)$$

(wherein R^1 is a lower alkyl group, a lower alkenyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, or a hydroxy-lower alkyl group, R^2 is a lower alkyl group, a cycloalkyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted phenyl-lower alkyl group, or a substituted or unsubstituted heteroaryl group, or R^1 and R^2 may combine together with the adjacent nitrogen atom to form a piperidine ring, a pyrrolidine ring, a morpholine ring, or a piperazine ring, and these rings may optionally be substituted by one or two lower alkyl groups, and R^3 is a hydrogen atom, a lower alkyl group, or a hydroxy-lower alkyl group);

Y is a hydrogen atom, a lower alkyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, a lower alkenyl group, a substituted or unsubstituted phenyl-lower alkyl group, or a group of the formula (Q):

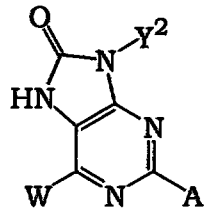
$-CH(R^3)CON(R^1)(R^2)$ (Q)

(wherein R^1, R^2 and R^3 are the same as defined above); and

A is a substituted or unsubstituted phenyl group, or a substituted or unsubstituted heteroaryl group;

provided that when one of X and Y of the above formula (I) is the group of the formula (Q), then the other is the same groups as defined for X or Y except for the group of the formula (Q),

and also provides an intermediate of the following formula (II):



(II)

wherein Y^2 is a hydrogen atom, a lower alkyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, a lower alkenyl group, or a substituted or unsubstituted phenyl-lower alkyl group; and

A and W are the same as those as defined above.

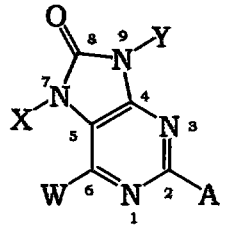
The pharmaceutically acceptable acid addition salt of the compound of the formula (I) includes a pharmaceutically acceptable acid addition salt of the compound of the formula (I) which shows basicity enough to form an acid addition salt thereof, for example, a salt with an inorganic acid such as hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc., or a salt with an organic acid such as maleate, fumarate, oxalate, citrate, tartrate, lactate, benzoate, methanesulfonate, etc.

The compound of the formula (I) and the intermediate thereof, i.e., the compound of the formula (II), and their acid addition acid salts

may exist in the form of a hydrate and/or a solvate, and the present invention also includes these hydrates and solvates as well.

The compound of the formula (I) may have one or more asymmetric carbon atoms, and by which stereoisomers thereof are possible, and the compound of the formula (I) may exist in a mixture of two or more stereoisomers. The present invention also includes these stereoisomers, a mixture thereof, and a racemic mixture thereof.

The positions of the purine nucleus of the 2-aryl-8-oxodihydropurine derivative of the present invention are numbered as shown in the following formula, and the compounds disclosed in the present specification are named according to these numbers.



(I)

wherein A, W, X and Y are the same as defined above.

The terms used in the present description and claims are explained below.

The lower alkyl group and the lower alkyl moiety include a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, unless defined otherwise. The "lower alkyl group" is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, and hexyl, but the preferable lower alkyl group is one having 1 to 4 carbon atoms. The "lower alkoxy group" includes an alkoxy group having 1 to 6 carbon atoms, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, etc. The "lower alkenyl group" includes ones having a double

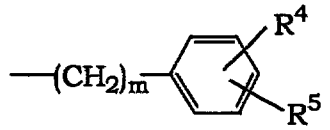
bond at any position except for between the 1- and 2-positions, and having 3 to 6 carbon atoms, for example, allyl, and 2-butenyl. The "cycloalkyl group" includes ones having 3 to 8 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The "cycloalkyl-lower alkyl group" includes an alkyl group having 1 to 4 carbon atoms which is substituted by one of the above mentioned "cycloalkyl groups", for example, cyclopropylmethyl, cyclopentylmethyl, and cyclohexylmethyl. The "hydroxy-lower alkyl group" includes a lower alkyl group being substituted by a hydroxy group, for example, hydroxymethyl, 2-hydroxyethyl, and 3-hydroxypropyl. The "halogen atom" is fluorine, chlorine, bromine, and iodine. The "mono- or di-lower alkylamino group" includes an amino group being substituted by one or two alkyl groups having 1 to 4 carbon atoms, for example, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, and ethylmethylamino.

The "substituted or unsubstituted phenyl group" includes a phenyl group which may optionally be substituted by one or two groups selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy group, an amino group, a mono- or di-lower alkylamino group, a cyano group and a nitro group, for example, phenyl; 2-, 3- or 4-chlorophenyl; 2-, 3- or 4-bromophenyl; 2-, 3- or 4-fluorophenyl; 2,4-dichlorophenyl; 2,4-dibromophenyl; 2,4-difluorophenyl; 2-, 3- or 4-methylphenyl; 2-, 3- or 4-methoxyphenyl; 2-, 3- or 4-trifluoromethylphenyl; 2-, 3- or 4-hydroxyphenyl; 2-, 3- or 4-aminophenyl; 2-, 3- or 4-methylaminophenyl; 2-, 3- or 4-dimethylaminophenyl; 2-, 3- or 4-cyanophenyl; and 2-, 3- or 4-

nitrophenyl.

The "substituted or unsubstituted phenyl-lower alkyl group" includes an alkyl group having 1 to 4 carbon atoms which is substituted by a phenyl group being optionally substituted by one or two groups selected from the group consisting of a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy group, an amino group, a mono- or di-lower alkylamino group, a cyano group and a nitro group, for example, benzyl; 2-, 3- or 4-chlorobenzyl; 2-, 3- or 4-bromobenzyl; 2-, 3- or 4-fluorobenzyl; 2,4-dichlorobenzyl; 2,4-dibromobenzyl; 2,4-difluorobenzyl; 2-, 3- or 4-methylbenzyl; 2-, 3- or 4-methoxybenzyl; 2-, 3- or 4-trifluoromethylbenzyl; 2-, 3- or 4-hydroxybenzyl; 2-, 3- or 4-aminobenzyl; 2-, 3- or 4-methylaminobenzyl; 2-, 3- or 4-dimethylaminobenzyl; 2-, 3- or 4-cyanobenzyl; 2-, 3- or 4-nitrobenzyl; phenethyl; and 2-(4-chlorophenyl)ethyl.

The examples of a group of the formula (A") as described below:

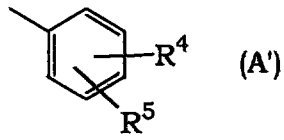


(A")

include the above-mentioned "substituted or unsubstituted phenyl group" or an alkyl group having 1 to 2 carbon atoms which is substituted by the above-mentioned "substituted or unsubstituted phenyl group", and more preferable ones are phenyl, 4- or 3-chlorophenyl, 4- or 3-bromophenyl, 4- or 3-fluorophenyl, 4-methoxyphenyl, 4-tirfluoromethylphenyl, 4-hydroxyphenyl, benzyl, 2-, 3- or 4-chlorobenzyl, 4-bromobenzyl, 3- or 4-fluorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, 4-trifluoromethylbenzyl, 4-hydroxybenzyl, phenethyl, and 2-(4-chlorophenyl)ethyl.

The "substituted or unsubstituted heteroaryl group" includes a 5-membered or 6-membered monocyclic heteroaryl group or a 5-membered or 6-membered bicyclic heteroaryl group, which may optionally be substituted by a C_1-C_3 alkyl group or a trifluoromethyl group, and has at least one of a nitrogen atom, an oxygen atom and a sulfur atom, for example, 2-, 3- or 4-pyridyl, 5-methyl-2-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-pyrazinyl, 1-pyrazolyl, 2-imidazolyl, 2-thiazolyl, 2-isoxazolyl, 5-methyl-3-isoxazolyl, quinolyl, and isoquinolyl.

Among the compounds of the present invention, the preferable one is a compound of the formula (I) wherein A is a group of the formula (A'):



(A')

(wherein R^4 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy group, an amino group, a mono- or di-lower alkylamino group, a cyano group, or a nitro group, and R^5 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, or a hydroxy group),

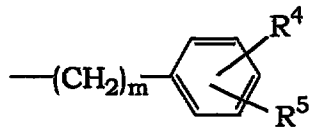
a pyridyl group, a thienyl group, or a furyl group, and W, X and Y are the same as defined above, or a pharmaceutically acceptable acid addition salt thereof.

The more preferable compounds are compounds of the formula (I) wherein

(a) X is a group of the formula (Qx):

$$-CH(R^{31})CON(R^{11})(R^{21}) \qquad (Qx)$$

wherein R^{11} is a lower alkyl group, and R^{21} is a lower alkyl group or a group of the formula (A"):



(A")

(wherein R^4 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy group, an amino group, a mono- or di-lower alkylamino group, a cyano group, or a nitro group, R^5 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, or a hydroxy group, and m is 0, 1 or 2), or

R^{11} and R^{21} may combine together with the adjacent nitrogen atom to form a piperidine ring, a pyrrolidine ring, a morpholine ring, or a piperazine ring, and these rings may optionally be substituted by one or two lower alkyl groups, and R^{31} is a hydrogen atom, a lower alkyl group, or a hydroxy-lower alkyl group, and

Y is a hydrogen atom or a lower alkyl group, or

(b) X is a hydrogen atom, a lower alkyl group, or a carbamoyl group, and

Y is a group of the formula (Qy):

$$-CH(R^{31})CON(R^{11})(R^{21}) \qquad (Qy)$$

wherein R^{11}, R^{21}, and R^{31} are the same as defined above,

A is the group of the above formula (A'), a pyridyl group, a thienyl group, or a furyl group, and W is the same as defined above, or a

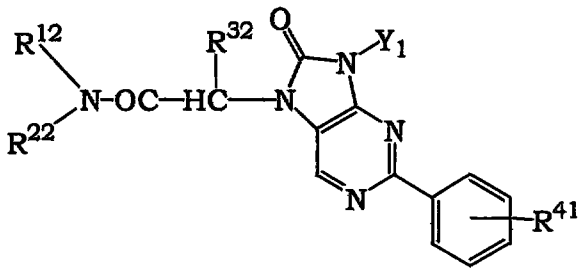
pharmaceutically acceptable acid addition salt thereof.

The further preferable compounds are compounds of the formula (I) wherein

(a) X is the group of the above formula (Qx) (wherein R^{11} is a methyl group, an ethyl group, a propyl group, an isopropyl group, or a butyl group, R^{21} is an ethyl group, a propyl group, an isopropyl group, a butyl group, a phenyl group, a phenyl group being substituted by a halogen, a methoxy, a trifluoromethyl, or a hydroxy, a benzyl group, or a benzyl group being substituted by a halogen, a methoxy, a trifluoromethyl, or a hydroxy, and R^{31} is the same as defined above), and Y is a hydrogen atom, a methyl group, or an ethyl group, or

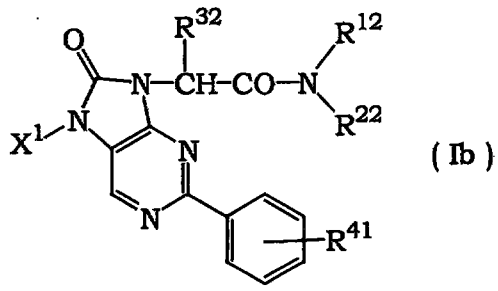
(b) X is a hydrogen atom, a methyl group, an ethyl group, a propyl group, an isopropyl group, or a butyl group, and Y is the group of the above formula (Qy) (wherein R^{11} is a methyl group, an ethyl group, a propyl group, an isopropyl group, or a butyl group, R^{21} is an ethyl group, a propyl group, an isopropyl group, a butyl group, a phenyl group, a phenyl group being substituted by a halogen, a methoxy, a trifluoromethyl, or a hydroxy, a benzyl group, or a benzyl group being substituted by a halogen, a methoxy, a trifluoromethyl, or a hydroxy, and R^{31} is the same as defined above), A is a group of the above formula (A'), a pyridyl group, a thienyl group, or a furyl group, and W is the same as defined above, or a pharmaceutically acceptable acid addition salt thereof.

The especially preferable compounds are 2-aryl-8-oxodihydropurine derivatives of the following formula (Ia) or (Ib), or a pharmaceutically acceptable acid addition salt thereof.



(Ia)

wherein R^{12} and R^{22} are the same or different, and each an ethyl group, a propyl group or a butyl group, or R^{12} is a methyl group, an ethyl group, or a propyl group, R^{22} is a phenyl group, a halogenophenyl group, a methoxyphenyl group, a benzyl group, a halogenobenzyl group, or a methoxybenzyl group, R^{32} is a hydrogen atom, a methyl group, or an ethyl group, Y^1 is a hydrogen atom, a methyl group, or an ethyl group, R^{41} is a hydrogen atom, a halogen atom, a methyl group, a methoxy group, a nitro group, or a trifluoromethyl group.



(Ib)

wherein X^1 is a hydrogen atom, a methyl group, an ethyl group, or a propyl group, R^{12} and R^{22} are the same or different, and each an ethyl group, a propyl group, or a butyl group, or R^{12} is a methyl group, an ethyl group, or a propyl group, and R^{22} is a phenyl group, a halogenophenyl group, a methoxyphenyl group, a benzyl group, a halogenobenzyl group, or a methoxybenzyl group, R^{32} is a hydrogen atom, a methyl group, or an ethyl group, and R^{41} is a hydrogen atom, a halogen atom, a methyl group, a methoxy group, a nitro group, or a trifluoro-

methyl group.

The compounds of the formula (Ia) or (Ib) wherein R^{32} is a hydrogen atom are more preferable.

The examples of the most preferable compound of the present invention are the following compounds, and pharmaceutically acceptable acid addition salts thereof.

N-ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide;

8,9-dihydro-9-methyl-N-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide;

8,9-dihydro-2-(4-fluorophenyl)-9-methyl-N-methyl-8-oxo-N-phenyl-7H-purin-7-acetamide;

N-ethyl-8,9-dihydro-2-(4-fluorophenyl)-9-methyl-8-oxo-N-phenyl-7H-purin-7-acetamide;

7,8-dihydro-7-methyl-8-oxo-2-phenyl-N,N-dipropyl-9H-purin-9-acetamide;

7-ethyl-7,8-dihydro-8-oxo-2-phenyl-N,N-dipropyl-9H-purin-9-acetamide;

N-benzyl-N-ethyl-7,8-dihydro-7-methyl-8-oxo-2-phenyl-9H-purin-9-acetamide;

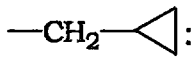
N-benzyl-7,8-dihydro-N-methyl-7-methyl-8-oxo-2-phenyl-9H-purin-9-acetamide;

N-benzyl-N-ethyl-7,8-dihydro-7-methyl-8-oxo-2-(4-chloro-phenyl)-9H-purin-9-acetamide;

N-benzyl-7,8-dihydro-N-methyl-7-methyl-8-oxo-2-(4-chloro-phenyl)-9H-purin-9-acetamide;

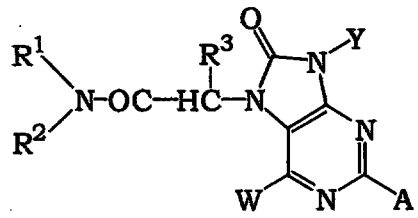
The representative compounds of the present invention are, in addition to the compounds of the following Examples, the compounds of the following formulae as listed in Tables 1 and 2, and a pharmaceutically acceptable acid addition salt thereof.

In Tables 1 and 2, the following Reference Examples and Examples, the following abbreviations are used in order to simplify the disclosure.

Me:	Methyl group
Et:	Ethyl group
Pr:	n-Propyl group
Bu:	n-Butyl group
Pent:	n-Pentyl group
 :	Cyclopropyl group
 :	Cyclopropylmethyl group
Bzl:	Benzyl group
Ph:	Phenyl group
Py:	Pyridyl group
Fur:	Furyl group
Thi:	Thienyl group

Thus, for example, Ph-4-Cl means 4-chlorophenyl group, and Ph-4-F means 4-fluorophenyl group, and 2-Thi means 2-thienyl group.

Table 1



R^1	R^2	R^3	A	Y	W
Et	Pr	H	Ph	Et	H
Et	Pr	$-CH_2OH$	Ph	Me	H
Pr	Pr	H	Ph	Me	Me
Pr	Pr	H	Ph-3-F	Me	H
Pr	Pr	Me	Ph	Me	H
Pr	Pr	H	4-Py	Me	H
Pr	Pr	H	2-Fur	Me	Me
Pr	Pr	H	Ph-3-Cl	Me	Me
Me	Ph	H	Ph-3-F	Me	H
Me	Ph	Me	Ph	Me	H
Me	Ph	$-CH_2OH$	Ph	Me	H
Me	Ph	H	Ph	Me	Me
Me	Ph	H	4-Py	Me	H
Me	Ph	H	3-Thi	Me	H
Me	Ph-3-F	H	Ph	Me	H
Me	Ph-4-Cl	H	Ph	Me	H

Table 1 (continued)

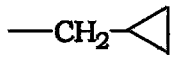
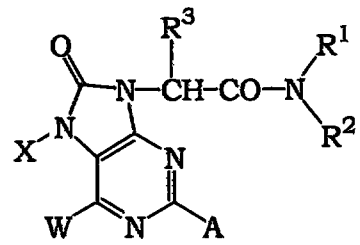
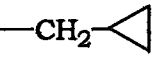
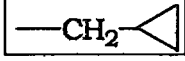
R^1	R^2	R^3	A	Y	W
Me	$-CH_2Ph$	H	3-Py	Me	H
Me	$-CH_2Ph$	H	Ph	Me	Me
Me	$-CH_2CH_2Ph$	H	Ph	Me	H
$-CH_2CH=CH_2$	$-CH_2Ph$	H	Ph	Me	H
Et	Ph	H	Ph		H
Et	Ph	H	Ph		H
Et	Ph	H	Ph-4-F	$-CH_2CH=CH_2$	H
Et	Ph	$-CH_2OH$	Ph	Me	H
Et	Ph	H	Ph-2-F	Me	Me
Et	Ph	H	Ph-3-F	Me	H
Et	Ph	H	Ph-4-F	Me	Me
Et	Ph	H	4-Py	Me	H
Et	Ph-2-F	H	Ph	Me	Me
Et	Ph-3-F	H	Ph	Me	H
Et	Ph-4-OMe	H	Ph-4-F	Me	H
Et	Ph	H	Ph	Me	Me
Et	Ph	H	Ph-2-Cl	Me	H
Et		H	Ph	Me	H

Table 2



R^1	R^2	R^3	A	X	W
Et	Pr	H	Ph	$-CONH_2$	H
Et	Pr	H	Ph-4-F	Me	H
Pr	Pr	Me	Ph	Me	H
Pr	Pr	H	Ph-4-F	Me	Me
Pr	Pr	H	Ph-3-F	$—CH_2$-cyclopropyl	H
Pr	Pr	H	Ph	$-CH_2CH=CH_2$	Me
Pr	Pr	$-CH_2OH$	Ph	H	H
Pr	Pr	H	Ph-4-Cl	$-CONH_2$	H
Pr	Pr	H	Ph-2-Cl	Me	H
Pr	Pr	$-CH_2OH$	Ph-4-F	H	Me
Pr	Pr	H	3-Py	H	H
Pr	Pr	H	3-Thi	Me	H

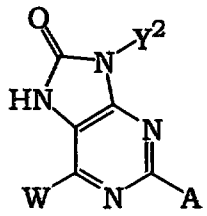
Table 2 (continued)

R^1	R^2	R^3	A	X	W
Pr	Pr	H	2-Fur	Et	Me
Me	Ph	H	Ph-4-F	H	H
Me	Ph-2-F	H	Ph	Me	H
Me	Ph-3-Cl	H	Ph	Me	H
Me	Ph	Me	Ph	Me	H
Me	Ph	H	Ph	Et	Me
Me	Ph	$-CH_2OH$	Ph-3-F	Me	H
Me	Ph	H	Ph	$-CONH_2$	H
Me	Ph	H	Ph		Me
Me	$-CH_2Ph$	H	4-Py	Et	H
Me	$-CH_2CH_2Ph$	H	Ph	Et	H
Et	Ph-3-Cl	H	Ph-4-F	H	H
Et	Ph-4-F	H	Ph	H	H
Et	Ph	Me	Ph-4-Cl	H	H
Et	Ph	H	Ph-4-F	Me	H
Et	Ph	H	Ph	$-CONH_2$	H
Et	Ph	H	3-Thi	H	H
Et	Ph	H	4-Py	Me	H
Pr	Ph	H	Ph-4-F	Me	H
Pr		H	Ph-4-Cl	Me	H
	$-CH_2Ph$	H	Ph	Me	H
	$-CH_2Ph$	H	Ph	Me	H

The compounds of the present invention may be prepared, for example, by the following processes.

Process (a)

The compound of the formula (I) wherein Y is a hydrogen atom, a lower alkyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, a lower alkenyl group, or a substituted or unsubstituted phenyl-lower alkyl group may be prepared by reacting a compound of the formula (II):



(II)

wherein A, W and Y^2 are the same as defined above, with a compound of the formula (III):

$$Z\text{-}CH(R^3)\text{-}CON(R^1)(R^2) \qquad \text{(III)}$$

wherein Z is a leaving atom or a leaving group, and R^1, R^2 and R^3 are the same as defined above.

The leaving atom or the leaving group represented by Z in the formula (III) includes an atom or a group which may be removed in the form of HZ together with the hydrogen atom of the NH moiety of the compound (II) under the reaction conditions, for example, a halogen atom (e.g., chlorine, bromine, iodine), a lower alkylsulfonyloxy group (e.g., methanesulfonyloxy), a trihalogenomethanesulfonyloxy group (e.g., trifluoromethanesulfonyloxy), and an arylsulfonyloxy group (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy).

The reaction of the compound (II) and the compound (III) is carried out in the presence of a base under atmospheric pressure or

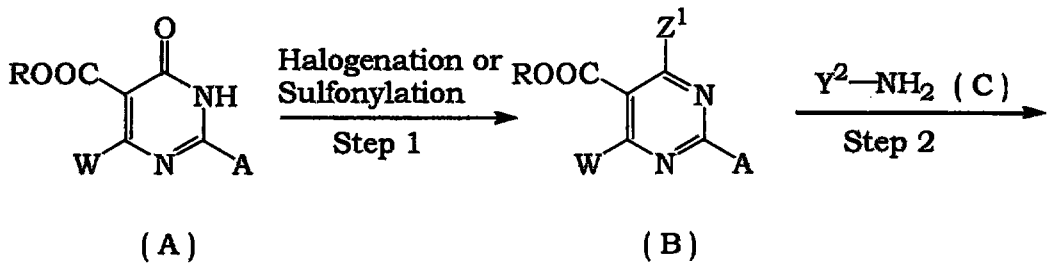
under pressure in a suitable solvent or without a solvent. The solvent includes, for example, toluene, xylene, dimethoxyethane, 1,2-dichloroethane, acetone, methyl ethyl ketone, dioxane, diglyme, ethyl acetate, dimethylformamide, and dimethylsulfoxide. The base includes, for example, sodium hydride, triethylamine, potassium carbonate, and sodium carbonate. The reaction is usually carried out at a temperature from about -10°C to about 150°C, preferably at a temperature from about 10°C to about 70°C.

When R^1 and/or R^3 of the formula (III) are a hydroxy-lower alkyl group, then said hydroxy-lower alkyl group may preferably be protected by a protecting group which can be removed by hydrogenolysis. Such protecting groups include, for example, benzyloxy, 4-chlorobenzyloxy, 3-bromobenzyloxy, 4-fluorobenzyloxy, 4-methylbenzyloxy, and 4-methoxybenzyloxy. These protecting groups may easily be converted into a hydroxy group by a conventional hydrogenolysis. Beside, when R^1 and/or R^3 in Processes (b) to (e) as described below are a hydroxy-lower alkyl group, it is preferable to protect these groups likewise, then to remove the protecting groups to give the desired compounds.

The compound of the formula (III) may be prepared by a conventional method, for example, by the method disclosed in Japanese Patent First Publication (Kokai) 64/1987, or a modified method thereof.

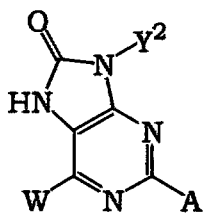
The starting compound (II) is prepared, for example, by the processes as shown in the following Route A or Route B.

Route A



(A) (B)

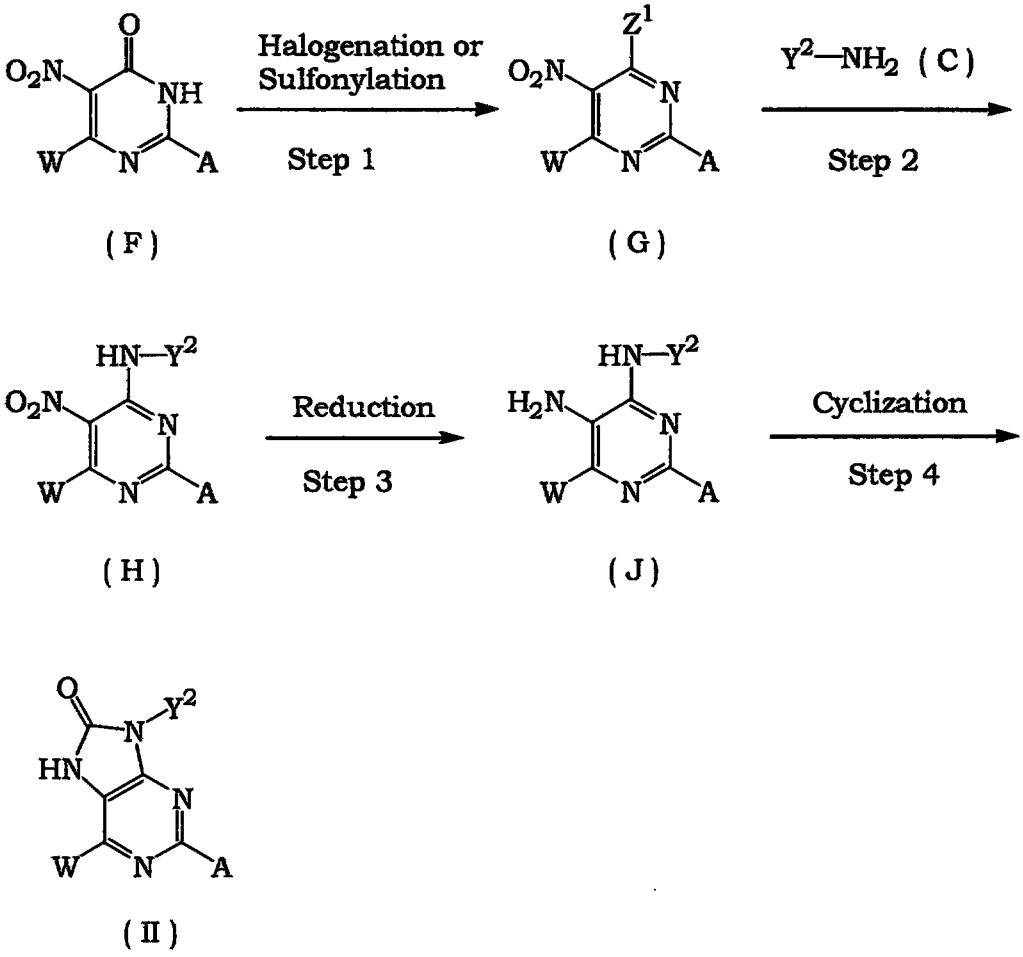
(D) (E)



(II)

wherein R is a lower alkyl group, Z^1 is a halogen atom, or an arylsulfonyloxy group or alkanesulfonyloxy group such as p-toluene-sulfonyloxy group, a methanesulfonyloxy group, or a trifluoromethane-sulfonyloxy group, and A, W and Y^2 are the same as defined above.

Route B



wherein A, W, Y^2 and Z^1 are the same as defined above.

Step 1: Halogenation or Sulfonylation

The halogenation is carried out by reacting the compound (A) or the compound (F) with a halogenating agent (e.g., phosphorus oxychloride, phosphorus tribromide). The sulfonylation is carried out, for example, by reacting the compound (A) or the compound (F) with a sulfonylating agent (e.g., methanesulfonyl chloride, p-toluenesulfonyl chloride, trifluoromethanesulfonyl chloride).

Step 2: Amination

The reaction of the compound (B) or the compound (G) with the compound (C) is carried out under atmospheric pressure or under pressure in a suitable solvent or without a solvent.

The solvent includes, for example, aromatic hydrocarbons (e.g., toluene, xylene), ketones (e.g., methyl ethyl ketone, methyl isobutyl ketone), ethers (e.g., dioxane, diglyme), alcohols (e.g., ethanol, isopropanol, butanol), acetonitrile, dimethylformamide, and dimethylsulfoxide. The reaction is preferably carried out in the presence of a base, and the base includes, for example, alkali metal carbonates (e.g., sodium carbonate, potassium carbonate), alkali metal hydrogen carbonates (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate), and tertiary amines (e.g., triethylamine), but the excess amount of the compound (C) may be used instead of a base. The reaction temperature varies according to the kinds of the starting compounds or the reaction conditions, but it is usually in the range of about 0°C to about 200°C, more preferably in the range of about 20°C to about 100°C.

Step 3 of Route A: Hydrolysis

The hydrolysis is carried out by a conventional method, for example, by contacting with water in a suitable solvent under acidic or basic conditions. The solvent includes, for example, alcohols (e.g., methanol, ethanol, isopropanol), dioxane, water, and a mixture of these solvents. The acid includes, for example, mineral acids (e.g., hydrochloric acid, sulfuric acid), and organic acids (e.g., formic acid, acetic acid, propionic acid, and oxalic acid). The base includes, for example,

alkali metal hydroxides (e.g., sodium hydroxide, potassium hydroxide), and alkali metal carbonates (e.g., sodium carbonate, potassium carbonate). The reaction is usually carried out at a temperature from about 20°C to 100°C.

Step 3 of Route B: Reduction

The reduction is carried out by a conventional method, for example, by reacting with hydrogen in a suitable solvent in the presence of a catalyst such as palladium-carbon, Raney nickel, platinum oxide, etc. The reduction is also carried out by using a combination of a metal (e.g., tin, zinc, iron) or a metal salt (e.g., stannous chloride) and an acid (e.g., hydrochloric acid, acetic acid), or by using iron or stannous chloride alone. The solvent includes, for example, alcohols (e.g., ethanol, methanol), water, acetic acid, dioxane, tetrahydrofuran. The reaction is usually carried out at a temperature from about 0°C to about 80°C, under atmospheric pressure or under pressure.

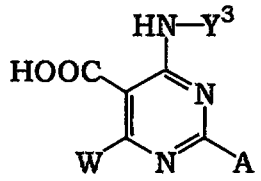
Step 4: Cyclization

The cyclization reaction is carried out in the same manner as explained in Process (b) or Process (C) as described below.

The starting compounds (A) and (F) may be commercially available ones, or can be prepared by a conventional method, for example, by the methods disclosed in J. Am. Chem. Soc., **74**, 842 (1952); Chem. Ber., **95**, 937 (1962); J. Org. Chem., **29**, 2887 (1964); J. Med. Chem., **35**, 4751 (1992); J. Org. Chem., **58**, 4490 (1993); Synthesis, 86 (1985), or the methods disclosed in Reference Examples 1, 11 and 15 as described below, or a modified method thereof.

Process (b)

The compound of the formula (I) wherein X is a hydrogen atom, and Y is a group of the formula (Q) is prepared by reacting a compound of the formula (IV):



(IV)

wherein Y^3 is the group represented by the above formula (Q), and A and W are the same as defined above, with an azide compound.

The azide compound used in this process includes, for example, diphenylphosphoryl azide, sodium azide.

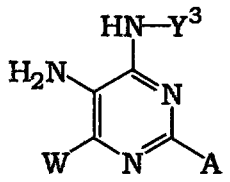
The reaction is carried out in the presence of a base under atmospheric pressure or under pressure in a suitable solvent or without a solvent. The solvent includes, for example, toluene, xylene, dimethoxyethane, 1,2-dichloroethane, acetone, methyl ethyl ketone, dioxane, diglyme, ethyl acetate, dimethylformamide, and dimethylsulfoxide. The base includes, for example, triethylamine, potassium carbonate, and sodium carbonate. The reaction is usually carried out at a temperature from about 10°C to about 150°C, preferably at a temperature from about 30°C to about 120°C.

The starting compound (IV) can be prepared by using the compound (C) in Route A that is Y^3-NH_2, and the compound (B), by the methods of Step 2 and Step 3 as shown in Route A. Moreover, the starting compound (IV) is also prepared by using the compound (B) in Route A and an amino acid, and introducing a substituted amino group

on the 4-position of the pyrimidine ring by the method of Step 2 of Route A, amidating thereof by the method disclosed in Process (e) as described below, and if necessary, by alkylating the product. The detailed procedures are explained in the following Reference Example 63.

Process (c)

The compound of the formula (I) wherein X is a hydrogen atom, and Y is a group of the formula (Q) is prepared by reacting a compound of the formula (V):



(V)

wherein A, W and Y^3 are the same as defined above, with urea, a carbonyldiimidazole or a diethyl carbonate.

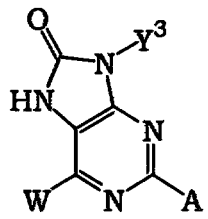
The reaction is carried out in a suitable solvent or without a solvent. The solvent includes, for example, tetrahydrofuran, toluene, dimethylsulfoxide, and ethyleneglycol. The reaction is usually carried out at a temperature from about 20°C to about 250°C, preferably at a temperature from about 60°C to about 220°C.

The starting compound (V) is prepared by using the compound (C) in Route B that is Y^3-NH_2, and the compound (G), by the methods of Step 2 and Step 3 as shown in Route B.

Process (d)

The compound (I) wherein X is a hydrogen atom or the groups other than the group of the formula (Q), and Y is the group of the

formula (Q) is prepared by reacting the compound (VI):



(VI)

wherein A, W and Y^3 are the same as defined above, which is obtained in the above Process (b), with a compound of the formula (VII):

$$Z\text{-}X^2 \qquad \text{(VII)}$$

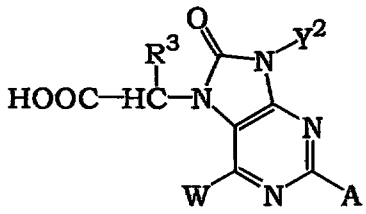
wherein X^2 is a hydrogen atom or the same groups for X except for the group of the formula (Q), and Z is the same as defined above.

The reaction is carried out in the same manner as in Process (a).

The starting compound (VII) may be commercially available ones, or can be prepared by a conventional method.

Process (e)

The compound (I) wherein X is a group of the formula (Q) is prepared by reacting a compound of the formula (VIII):



(VIII)

wherein A, R^3, W and Y^2 are the same as defined above, or a reactive derivative thereof, with a compound of the formula (IX):

$$HN(R^{13})(R^{23}) \qquad \text{(IX)}$$

wherein R^{13} and R^{23} are each a hydrogen atom or the same groups for R^1 and R^2 as defined above, respectively, and when one of R^{13} and R^{23} is a hydrogen atom, then further reacting the product with a compound of

the formula (X):

$$R^{24}\text{-}Z \qquad (X)$$

or the formula (XI):

$$R^{14}\text{-}Z \qquad (XI)$$

wherein R^{24} is a lower alkyl group, a cycloalkyl group, or a substituted or unsubstituted phenyl-lower alkyl group, R^{14} is a lower alkyl group, a lower alkenyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, or a hydroxy-lower alkyl group, and Z is the same as defined above,

provided that when R^{13} is a hydrogen atom, then reacting with the compound (X), and when R^{23} is a hydrogen atom, then reacting with the compound (XI).

The reactive derivative of the compound (VIII) includes, for example, a lower alkyl ester (especially, methyl ester), an active ester, an acid anhydride, and an acid halide (especially, an acid chloride). The active ester includes, for example, p-nitrophenyl ester, 2,4,5-trichlorophenyl ester, and N-hydroxysuccinimide ester. The acid anhydride includes, for example, a symmetric acid anhydride and a mixed acid anhydride. The mixed acid anhydride includes, for example, a mixed acid anhydride with an alkyl chlorocarbonate such as ethyl chlorocarbonate, and isobutyl chlorocarbonate, a mixed acid anhydride with an aralkyl chlorocarbonate such as benzyl chlorocarbonate, a mixed acid anhydride with an aryl chlorocarbonate such as phenyl chlorocarbonate, and a mixed acid anhydride with an alkanoic acid such as isovaleric acid and pivalic acid.

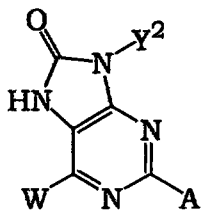
When the compound (VIII) per se is used, the reaction can be

carried out in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride, N,N'-carbonyldiimidazole, N,N'-carbonyl-disuccinimide, 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, diphenylphosphoryl azide, propanesulfonic anhydride, and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium · hexafluorophosphate.

The reaction of the compound (VIII) or a reactive derivative thereof with the compound (IX) is carried out in a solvent or without a solvent. The solvent varies according to the kinds of the starting compounds, etc., and includes, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene), ethers (e.g., diethyl ether, tetrahydrofuran, dioxane), halogenated hydrocarbons (e.g., methylene chloride, chloroform), alcohols (e.g., ethanol, isopropanol), ethyl acetate, acetone, acetonitrile, dimethylformamide, dimethylsulfoxide, ethylene glycol, water, etc., and these solvents may be used alone, or in the form of a mixture of two or more solvents. The reaction is carried out in the presence of a base if necessary, and the base includes, for example, alkali metal hydroxides (e.g., sodium hydroxide, potassium hydroxide), alkali metal carbonates (e.g., sodium carbonate, potassium carbonate), alkali metal hydrogen carbonates (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate), and organic bases such as triethylamine, tributylamine, diisopropylethylamine, N-methylmorpholine, but the excess amount of the compound (IX) may be used instead of a base. The reaction temperature varies according to the kinds of the starting compounds, but it is usually in the range of about -30°C to about 200°C, preferably in the range of about -10°C to about 150°C.

The reaction of the product obtained in the reaction between the compound (VIII) and the compound (IX), and the compound (X) or the compound (XI) is carried out by the method described in the above Process (a).

The compound (VIII) is prepared by reacting a compound of the formula (II):



(II)

wherein A, W and Y^2 are the same as defined above, with a compound of the formula (XII):

$$Z^1\text{-}CH(R^3)\text{-}COOR \qquad (XII)$$

wherein R, R^3 and Z^1 are the same as defined above, followed by subjecting the product to hydrolysis in a conventional manner.

The reaction is carried out in the same manner as in Process (a).

The compound (X) and the compound (XI) may be commercially available ones, or can be prepared by a conventional method.

The present compounds can also be prepared by the following methods.

The compound (I) wherein W is a lower alkoxy group is prepared by reacting a compound of the formula (I) wherein W is a halogen atom with a metal lower alkylate, and the detailed procedures thereof are explained in Example 46.

The compound (I) wherein W is a mono- or di-lower alkylamino group is prepared by reacting a compound of the formula (I) wherein W

is a halogen atom with a mono- or di-lower alkylamine, and the detailed procedures thereof are explained in Example 47.

The compound (I) wherein the phenyl group is substituted by a hydroxy group is prepared by treating a compound of the formula (I) wherein the phenyl group is substituted by a methoxy group with boron tribromide or hydrogen bromide, and the detailed procedures thereof are explained in Example 174.

The desired compounds obtained in the above Processes can be isolated and purified by a conventional method such as chromatography, recrystallization, re-precipitation, etc. The compound (I) which shows basicity enough to form an acid addition salt thereof is converted into an acid addition salt thereof by treating it with various acids by a conventional method.

Various stereoisomers of the compound (I) can be separated and purified by a conventional method such as chromatography, etc.

The pharmacological activities of the present compounds are explained by the following pharmacological experiments on the representative compounds of the present invention.

Experiment 1: Central (ω_1,ω_2) and peripheral (ω_3) benzodiazepine receptor binding assays

$BZ\omega_1$ and $BZ\omega_2$ receptor binding assays and the preparation of receptor membrane fractions therefor were carried out according to the method of Stephens, D. N. et al. [cf., J. Pharmacol. Exp. Ther., **253**, 334-343 (1990)], and $BZ\omega_3$ receptor binding assay and the preparation of receptor membrane fraction therefor were done according to the method of Schoemaker, H. [cf., J. Pharmacol. Exp. Ther., **225**, 61-69

(1983)] each with slight modification.

Receptor membrane fractions for ω_1, ω_2 and ω_3 were prepared from the cerebellum (ω_1), spinal cord (ω_2) or kidney (ω_3) in 7-8 week old male rats of Wistar strain, respectively, by the procedure described below.

After the cerebellum or spinal cord was homogenized with 20 volumes of ice-cold 50 mM Tris-citrate buffer (pH 7.1), the homogenate was centrifuged for 15 minutes at 40,000 g. The pellet obtained was washed 4 times by the same procedure, and frozen and stored for 24 hours at -60°C. The resulting pellet, after being thawed, washed with the buffer and centrifuged, was suspended in the buffer I for the binding assay (50 mM Tris-HCl buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$; pH 7.4) and the suspension thus obtained (containing 1 g wet tissue/40 ml) was used for the $BZ\omega_1$ and $BZ\omega_2$ receptor binding assays. On the other hand, the kidney was homogenized with 20 volumes of the ice-cold buffer II for the binding assay (50 mM Na-K phosphate buffer containing 100 mM NaCl; pH 7.4), and the mixture was filtered through 4 sheets of gauze, and centrifuged for 20 minutes at 40,000 g. The pellet obtained was suspended in the buffer II and the suspension (containing 1 g wet tissue/100 ml) was used for the binding assay as $BZ\omega_3$ receptor membrane source.

[^{3}H] Flumazenil (Ro 15-1788) (final concentration: 0.3 nM for ω_1, and 1 nM for ω_2) and flunitrazepam (final concentration: 10 μM) were used for the $BZ\omega_1$ or $BZ\omega_2$ receptor binding assays as the isotope-labeled and unlabeled ligands, respectively. For the $BZ\omega_3$ receptor binding assay, [^{3}H] 4'-chlorodiazepam (7-chloro-1,3-dihydro-1-methyl-5-

(4-chlorophenyl)-2H-1,4-diazepin-2-one) (Ro 5-4864) (final concentration: 0.5 nM) and diazepam (final concentration: 100 μM) were used as the isotope-labeled and unlabeled ligands, respectively. Incubation was performed for 30 minutes at 37°C in the $BZ\omega_1$ or $BZ\omega_2$ receptor binding assays, and for 150 minutes at 0°C in the $BZ\omega_3$ receptor binding assay. The $BZ\omega_1$ or $BZ\omega_2$ receptor binding assays were carried out in the presence of bicuculline (final concentration: 100 μM).

The binding assay was performed by the following procedure. After adding each test compound at certain known concentrations, a [^{3}H] ligand, and the buffer I or II to each test tube, each assay was started by addition of membrane preparation (total volume of 1 ml). After incubation, the assay was terminated by filtration with suction through a Whatman GF/B glass fiber filter using a cell harvester (Brandel, USA). The filters were rapidly washed 3 times with 5 ml of ice-cold 50 mM Tris-HCl buffer (pH 7.7) for ω_1 and ω_2, or the buffer II for ω_3, and transferred to scintillation vials containing 10 ml liquid scintillation cocktail (ACS-II, Amersham, USA). After being allowed to stand for a specific period, retained radioactivity was counted by a liquid scintillation spectrometer. Specific binding of [^{3}H] ligands was calculated as the difference between amounts of radioactivity bound in the presence and absence of excess unlabeled ligands. The concentration of the test compounds causing 50% inhibition of specific binding of the [^{3}H] ligand (IC_{50}) was determined by probit analysis. The results are shown in Table 3. It is noted that all the compounds as listed in Table 5 had affinity for the $BZ\omega_1$ and $BZ\omega_2$ receptors with IC_{50}

values larger than 1000 nM.

Table 3

Test Comp.	ω_3 IC_{50}(nM)	Test Comp.	ω_3 IC_{50}(nM)
1*	2.0	83	1.3
2	1.2	94	2.7
4	1.6	97	0.35
5	1.3	99	1.4
6	2.0	101	1.3
10	1.0	103	0.8
11	2.4	106	1.2
12	1.5	107	0.66
13	2.9	112	0.73
26	2.3	113	0.97
29	4.5	114	0.97
37	2.8	116	2.1
39	1.3	136	0.66
40	1.6	137	1.3
48	0.68	140	0.87
49	1.4	146	0.85
50	0.79	147	1.1
51	1.2	150	0.81
54	0.83	151	2.3
56	1.4	156	0.67
69	0.55	157	1.1
71	0.43	161	1.1
73	1.7	162	1.1
74	0.99	163	0.73
75	1.3	166	1.2
77	2.4	170	1.8
81	5.0	172	3.5

*: The compound of Example 1 (hereinafter, the test compound numbers mean the compounds of the corresponding Examples in the same way)

The compounds listed in Table 3 strongly bind to the $BZ\omega_3$ receptor, but had affinity for the $BZ\omega_1$ and $BZ\omega_2$ receptors with the IC_{50} value larger than 1000 nM. Therefore, it is apparent that the compounds of the present invention have potent and highly selective affinity for the $BZ\omega_3$ receptor.

Experiment 2: Light and dark box test (anti-anxiety effect)

Anti-anxiety effect of test compounds was examined in a box with light and dark compartments according to the method of Crawley, J. and Goodwin, F.K. [cf., Pharmacol. Biochem. Behav., **13**, 167-170 (1980)] with slight modification.

Light and dark box test is a useful, simple and handy method for behaviorally and pharmacologically examining anti-anxiety effect of the drugs, by utilizing the habit of rodents such as mice and rats, etc. which prefer to stay in a dark place, and regarding as positive drug effect the increase of the relative stay of the animals in the light compartment which is an uncomfortable place for the animals. A number of drugs such as cholecystokinin B type receptor antagonists and benzodiazepine drugs, show positive effect in this test.

Light and dark box test was carried out using the test box device (35 X 17 X 15 cm) which comprises: a light compartment (20 X 17 X 15 cm) consisting of transparent acrylic plates and highly illuminated by an incandescent lamp (1,700 lux); a dark compartment (15 X 17 X 15 cm) being made of black acrylic plates connected to the light compartment; and at the boundary of compartments, an opening (4.4 X 5.0 cm) in which mice can go through freely between two compartments.

Male mice of Std-ddY strain weighing 25-30 g were used in a group of 10. Each trial was started by placing a mouse in the center of the light compartment 30 minutes after oral administration of a test compound, and the time spent by the mouse in the light compartment during a 5 minute observation period was measured, and the rate of the stay of mice in the light compartment to the whole time spent in the experiment was calculated (rate of light compartment stay, %).

The anti-anxiety effect of the test compound was represented by the minimum effective dose (MED) at which the increasing rate of the relative stay in the light compartment was regarded as statistically significant (Dunnetp test, significance level: 5 %). The results are shown in Table 4.

Table 4

Test Comp.	Anti-anxiety effect
	MED (mg/kg)
1*	0.001
2	0.001
5	0.001
12	0.01
28	0.01
30	1.0
50	0.1
106	0.001
107	0.001
116	0.01
136	0.003
137	0.001
146	0.003
147	0.001
163	0.1

*: The compound of Example 1 (hereinafter, the test compound numbers mean the compounds of the corresponding Examples in the same way)

The present compounds as listed in Table 4 showed anti-anxiety effect at doses of 1 mg/kg or below, and especially the compounds of Examples 1, 2, 5, 106, 107, 136, 137, 146 and 147 showed anti-anxiety effect even at a low dose of 0.001-0.003 mg/kg.

Experiment 3: Isoniazid-induced clonic convulsion test (anti-convulsant effect)

Isoniazid inhibits glutamate decarboxylase that catalyzes GABA biosynthesis, decreases brain GABA levels, and induces clonic

convulsion. According to the method of Auta, J. et al. [cf., J. Pharmacol. Exp. Ther., **265**, 649-656 (1993)] with slight modification, antagonistic effects of the test compounds on isoniazid-induced clonic convulsion were examined. Many drugs, which directly or indirectly enhance $GABA_A$ receptor function, are known to exhibit positive effect in this test. Such drugs are BZ receptor agonists represented by diazepam, neurosteroids such as allopregnanolone, allotetrahydro-deoxycorticosterone (THDOC) and $BZ\omega_3$ receptor agonists, which enhance the synthesis of neurosteroids.

Male mice of Std-ddY strain weighing 22-24 g were used in a group of 6. Thirty minutes after oral administration of the test compounds, mice were injected with isoniazid (200 mg/kg) subcutaneously, and immediately thereafter, the mice were placed individually in plastic observation cages. The onset time of clonic convulsion was measured (cut-off time: 90 minutes). The latency in the control group was about 40 minutes.

Anti-isoniazid effect of the test compounds was expressed by the dose, which prolonged the onset time by 25% compared to that in the vehicle group (ED_{25}). The ED_{25} value was calculated according to the Probit method. The results are shown in Table 5.

Table 5

Test Comp.	Anti-convulsant effect
	ED_{25} (mg/kg)
106*	100
107	33.0
110	51.0
112	73.6

*: The compound of Example 106 (hereinafter, the test compound numbers mean the compounds of the corresponding Examples in the same way)

Experiment 4: Acute toxicity

Male mice of Std-ddY strain weighing 25-30 g were used in a group of 10 animals for examining on the compound of Example 1. A test compound was suspended in 0.5% tragacanth and administered orally to the mice at a dose of 2000 mg/kg. Then, lethality of the mice was observed for 7 days after the treatment, and no lethality was found in mice to which the compound of Example 1 was administered.

As is shown in the results of the above pharmacological experiments, the compounds of formula (I) not only show a selective and remarkable affinity for $BZ\omega_3$-receptor *in vitro*, but also show excellent pharmacological activities such as anti-anxiety effect and anti-convulsant effect, etc. in animal experiments, therefore, they are useful for prophylaxis or treatment of central nervous disorders such as anxiety-related diseases (neurosis, somatoform disorders, anxiety disorders, and others), depression, epilepsy, etc. , immuno-neurologic diseases (multiple sclerosis, etc.), and circulatory organs disorders (angina pectoris, hypertension, etc.).

As the compounds showing a selective and remarkable affinity

for BZ_{ω_3} receptor as well as showing potent anti-anxiety activity, the following compounds and pharmaceutically acceptable acid addition salts thereof are exemplified.

(1) N-ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide (the compound of Example 1)

(2) 8,9-dihydro-9-methyl-N-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide (the compound of Example 2)

(3) 8,9-dihydro-2-(4-fluorophenyl)-9-methyl-N-methyl-8-oxo-N-phenyl-7H-purin-7-acetamide (the compound of Example 5)

(4) N-ethyl-8,9-dihydro-2-(4-fluorophenyl)-9-methyl-8-oxo-N-phenyl-7H-purin-7-acetamide (the compound of Example 12)

(5) 7,8-dihydro-7-methyl-8-oxo-2-phenyl-N,N-dipropyl-9H-purin-9-acetamide (the compound of Example 106)

(6) 7-ethyl-7,8-dihydro-8-oxo-2-phenyl-N,N-dipropyl-9H-purin-9-acetamide (the compound of Example 107)

(7) N-benzyl-N-ethyl-7,8-dihydro-7-methyl-8-oxo-2-phenyl-9H-purin-9-acetamide (the compound of Example 146)

(8) N-benzyl-7,8-dihydro-N-methyl-7-methyl-8-oxo-2-phenyl-9H-purin-9-acetamide (the compound of Example 136)

(9) N-benzyl-N-ethyl-7,8-dihydro-7-methyl-8-oxo-2-(4-chlorophenyl)-9H-purin-9-acetamide (the compound of Example 147)

(10) N-benzyl-7,8-dihydro-N-methyl-7-methyl-8-oxo-2-(4-chlorophenyl)-9H-purin-9-acetamide (the compound of Example 137)

The compounds of the present invention can be administered either orally, parenterally or rectally. The dose of the compounds of the present invention varies according to the kinds of the compound, the

administration routes, the conditions, ages of the patients, etc., but it is usually in the range of 0.01-50 mg/kg/day, preferably in the range of 0.03-5 mg/kg/day.

The compounds of the present invention are usually administered in the form of a pharmaceutical preparation, which is prepared by mixing thereof with a pharmaceutically acceptable carrier or diluent. The pharmaceutically acceptable carrier or diluent may be any conventional ones, which are usually used in the pharmaceutical field, and do not react with the compounds of the present invention. Suitable examples of the pharmaceutically acceptable carrier or diluent are, for example, lactose, inositol, glucose, mannitol, dextran, cyclodextrin, sorbitol, starch, partly pregelatinized starch, white sugar, magnesium metasilicate aluminate, synthetic aluminum silicate, crystalline cellulose, sodium carboxymethylcellulose, hydroxypropyl starch, calcium carboxylmethylcellulose, ion exchange resin, methylcellulose, gelatin, gum arabic, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, alginic acid, sodium alginate, light anhydrous silicic acid, magnesium stearate, talc, carboxyvinyl polymer, titanium oxide, sorbitan fatty acid ester, sodium laurylsulfate, glycerin, glycerin fatty acid ester, purified lanolin, glycerogelatin, polysorbate, macrogol, vegetable oil, wax, propyleneglycol, water, ethanol, polyoxyethylene-hydrogenated caster oil (HCO), sodium chloride, sodium hydroxide, hydrochloric acid, disodium hydrogen phosphate, sodium dihydrogen phosphate, citric acid, glutamic acid, benzyl alcohol, methyl p-oxybenzoate, ethyl p-oxybenzoate, etc.

The pharmaceutical preparation is, for example, tablets, capsules, granules, powders, syrups, suspensions, suppositories, injection preparations, etc. These preparations may be prepared by a conventional method. In the preparation of liquids, the compound of the present invention may be dissolved or suspended in water or a suitable other solvent, when administered. Tablets and granules may be coated by a conventional method. In the injection preparations, it is preferable to dissolve the compound of the present invention in water, but if necessary, it may be dissolved by using an isotonic agent or a solubilizer, and further, a pH adjuster, a buffering agent or a preservative may be added thereto.

These preparations may contain the compound of the present invention at a ratio of at least 0.01 %, preferably at a ratio of 0.1-70 %. These preparations may also contain other therapeutically effective compounds as well.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated in more detail by the following Reference Examples and Examples, but should not be construed to be limited thereto.

The identification of the compounds is carried out by Elementary analysis, Mass spectrum, IR spectrum, NMR spectrum, etc.

The following abbreviations may be used in the following Reference Examples and Examples in order to simplify the description.

[Solvent for recrystallization]

A: Ethanol

AN: Acetonitrile

CF: Chloroform

E: Diethyl ether

M: Methanol

IP: Isopropanol

IPE: Diisopropyl ether

DMF: Dimethylformamide

Reference Example 1

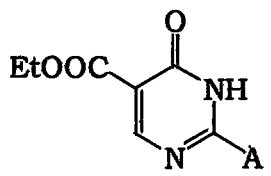
Preparation of ethyl 3,4-dihydro-4-oxo-2-phenylpyrimidine-5-carboxylate:

To a mixture of sodium methoxide (16.5 g) and anhydrous ethanol (200 ml) is added benzamidine hydrochloride (16 g) at 0-5°C. The mixture is stirred at 0°C for 30 minutes, and thereto is added dropwise a solution of diethyl ethoxymethylenemalonate (20 g) in anhydrous ethanol (50 ml) at the same temperature. After the addition, the mixture is stirred at room temperature for 30 minutes, and refluxed for 6 hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in water. To the mixture is added with stirring and drowpise hydrochloric acid at 0-5°C until the pH value of the mixture is adjusted to pH 4. The precipitates are collected by filtration, washed with water, washed with diethyl ether, and washed with ethanol to give the desired compound (17.5 g).

Reference Examples 2-10

The corresponding starting compounds are treated in the same manner as in Reference Example 1 to give the compounds as listed in Table 6.

Table 6



Reference Ex.	A
2	Ph-3-Cl
3	Ph-4-Cl
4	Ph-4-F
5	Ph-4-OMe
6	Ph-4-NO_2
7	Ph-4-Me
8	3-Pyriyl
9	2-Thienyl
10	3-Thienyl

Reference Example 11

Preparation of ethyl 3,4-dihydro-4-oxo-2,6-diphenylpyrimidine-5-carboxylate:

(1) To a mixture of a 20 % solution of sodium ethoxide in ethanol (44.9 g) and ethanol (200 ml) is added benzamidine hydrochloride (10.3 g) at room temperature. The mixture is stirred at the same temperature for two hours, and thereto is added ethyl benzalmalonate (14.9 g), and the mixture is refluxed for three hours. The reaction mixture is concentrated under reduced pressure, and to the residue is added ice-water. To the mixture is added dropwise conc. hydrochloric acid until the pH value of the mixture is adjusted to pH 4. The precipitates are collected by filtration, and washed with water to give crude ethyl 3,4,5,6-tetrahydro-4-oxo-2,6-diphenylpyrimidine-5-

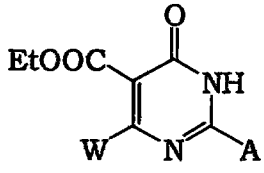
carboxylate (15.8 g).

(2) A mixture of the above compound (15.5 g), 2,3-dichloro-2,3-dicyano-p-benzoquinone (13.6 g) and ethanol (300 ml) is stirred at room temperature for four hours. The reaction mixture is concentrated under reduced pressure, and thereto are added water and chloroform. The chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; chloroform), and diisopropyl ether is added to the resultant. The precipitates are collected by filtration to give the desired compound (10.7 g).

Reference Examples 12-14

The corresponding starting compounds are treated in the same manner as in Reference Example 11 to give the compounds as listed in Table 7.

Table 7



Reference Ex.	W	A
12	Me	Ph-4-CF_3
13	Ph	Ph-4-CF_3
14	Ph-4-CF_3	Ph

Reference Example 15

Preparation of 5-nitro-2-phenyl-4(3H)-pyrimidinone:

To a mixture of sodium methoxide (8 g) and anhydrous ethanol

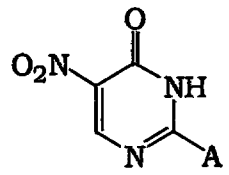
(100 ml) is added benzamidine hydrochloride (11.7 g) at 0°C. The mixture is stirred at 0°C for 30 minutes, and thereto is added dropwise a solution of crude ethyl 2-(N,N-dimethylaminomethylene)nitroacetate (14 g, which is obtained by heating a mixture of ethyl nitroacetate (10 g) and N,N-dimethylformamide dimethyl acetal (10.7 g) under reflux for three hours, followed by concentrating the mixture under reduced pressure) in anhydrous ethanol (50 ml) at the same temperature. After the addition, the mixture is stirred at room temperature for 30 minutes, and refluxed for 12 hours. The reaction mixture is concentrated under reduced pressure, and to the resultant is added water (150 ml). To the mixture is added dropwise conc. hydrochloric acid at 0°C until the pH value of the mixture is adjusted to pH 4. The precipitates are collected by filtration, washed with water, and recrystallized from ethanol to give the desired compound (7 g).

M.p. 264-266°C.

Reference Examples 16-18

The corresponding starting compounds are treated in the same manner as in Reference Example 15 to give the compounds as listed in Table 8.

Table 8



Reference Ex.	A	M.p.(°C)	Solvent for recrystallization
16	Ph-4-Cl	218-221	Ethanol
17	Ph-3-CF_3	143-145	Ethanol
18	Ph-4-CF_3	185-188	Methanol

Reference Example 19

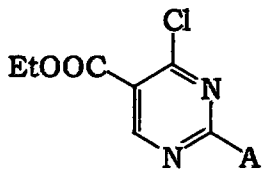
Preparation of ethyl 4-chloro-2-phenylpyrimidine-5-carboxylate:

A mixture of ethyl 3,4-dihydro-4-oxo-2-phenylpyrimidine-5-carboxylate (12 g) and phosphorus oxychloride (22.6 g) is stirred at 90°C for four hours. The reaction mixture is poured into ice-water, and the mixture is neutralized with 1N aqueous sodium hydroxide solution. The precipitates are collected by filtration, and washed with water to give the desired compound (11 g).

Reference Examples 20-28

The corresponding starting compounds are treated in the same manner as in Reference Example 19 to give the compounds as listed in Table 9.

Table 9



Reference Ex.	A
20	Ph-3-Cl
21	Ph-4-Cl
22	Ph-4-F
23	Ph-4-OMe
24	Ph-4-NO_2
25	Ph-4-Me
26	3-Pyridyl
27	2-Thienyl
28	3-Thienyl

Reference Example 29

Preparation of 4-chloro-5-nitro-2-phenylpyrimidine:

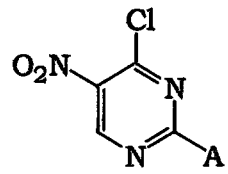
A mixture of 5-nitro-2-phenyl-4(3H)-pyrimidinone (6 g) and phosphorus oxychloride (8.5 g) is stirred at 90°C for four hours. After cooling, the reaction mixture is concentrated under reduced pressure, and the residue is dissolved in chloroform. To the mixture is added ice-water, and the mixture is stirred. The mixture is neutralized with 1N aqueous sodium hydroxide solution, and the chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is recrystallized from ethanol to give the desired compound (5.6 g).

M.p. 160-161°C.

Reference Examples 30-32

The corresponding starting compounds are treated in the same manner as in Reference Example 29 to give the compounds as listed in Table 10.

Table 10



Reference Ex.	A	M.p. (°C)	Solvent for recrystal.
30	Ph-4-Cl	144-146	Isopropanol
31	Ph-3-CF_3	89-90	Isopropanol
32	Ph-4-CF_3	77-78	Isopropanol

Reference Example 33

Preparation of 4,6-dichloro-5-nitro-2-phenylpyrimidine:

(1) Using a 20 % solution of sodium ethoxide in ethanol (150 g), benzamidine hydrochloride (34.5 g), diethyl malonate (32 g) and ethanol (500 ml), the same procedures as Reference Example 11-(1) are repeated to give crude 4,6-dihydroxy-2-phenylpyrimidine (31.5 g).

(2) To 90 % nitric acid (150 ml) is added the above compound (30 g) in portions at 0-5°C, and the mixture is stirred at room temperature for 30 minutes. The reaction mixture is poured into ice-water, and the precipitates are collected by filtration, and washed with water to give crude 4,6-dihydroxy-5-nitro-2-phenylpyrimidine (32 g).

(3) To a mixture of the above compound (8 g) and dimethylaniline (4 g) is added dropwise phosphorus oxychloride at room temperature.

After the addition, the mixture is refluxed for three hours, and the reaction mixture is poured into ice-water. The precipitates are collected by filtration, and washed with water to give the desired compound (8.7 g).

Reference Example 34

Preparation of 4-methylamino-2-phenylpyrimidine-5-carboxylic acid:

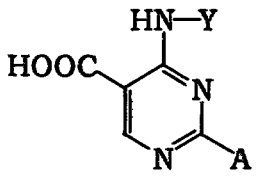
(1) A mixture of ethyl 4-chloro-2-phenylpyrimidine-5-carboxylate (10 g), methylamine hydrochloride (2.8 g), triethylamine (8.5 g) and isopropanol (100 ml) is refluxed for six hours. The reaction mixture is concentrated under reduced pressure, and to the residue are added chloroform and water. The chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give ethyl 4-methylamino-2-phenylpyrimidine-5-carboxylate (8 g).

(2) A mixture of the above compound (8 g), 1N aqueous sodium hydroxide solution (150 ml) and ethanol (50 ml) is refluxed for two hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in ice-water, and thereto is added conc. hydrochloric acid until the pH value of the mixture is adjusted to pH 1. The precipitated crystals are collected by filtration, washed with water, and washed with ethanol to give the desired compound (7.3 g).

Reference Examples 35-50

The corresponding starting compounds are treated in the same manner as in Reference Example 34 to give the compounds as listed in Table 11.

Table 11



Reference Ex.	Y	A
35	Me	Ph-3-Cl
36	Me	Ph-4-Cl
37	Me	Ph-4-F
38	Me	Ph-4-OMe
39	Me	Ph-4-NO_2
40	Me	Ph-4-Me
41	Me	3-Pyridyl
42	Me	2-Thienyl
43	Me	3-Thienyl
44	-CH_2Ph	Ph
45	-$CH_2CON(Pr)_2$	Ph
46	-$CH_2CON(Pr)_2$	Ph-3-Cl
47	-$CH_2CON(Pr)_2$	Ph-4-F
48	-$CH_2CON(Pr)_2$	Ph-4-OMe
49	-$CH_2CON(Pr)_2$	Ph-4-NO_2
50	-CH_2CON(Me)Ph	3-Pyridyl

Reference Example 51

Preparation of 2-phenyl-4-propylaminopyrimidine-5-carboxylic acid:

(1) A mixture of ethyl 3,4-dihydro-4-oxo-2-phenylpyrimidine-5-carboxylate (9.8 g), triethylamine (10.1 g) and dimethylformamide (20 ml) is added dropwise a solution of p-toluenesulfonyl chloride (8.4 g) in dimethylformamide (20 ml) at room temperature, and the mixture is stirred at the same temperature for 10 minutes. To the reaction

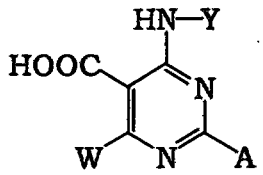
mixture is added dropwise a solution of propylamine (2.8 g) in dimethylformamide (20 ml), and the mixture is stirred at room temperature for one hour. To the reaction mixture are added chloroform and water, and the chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give crude ethyl 2-phenyl-4-propylaminopyrimidine-5-carboxylate (11 g).

(2) A mixture of the above compound (11 g), 1N aqueous sodium hydroxide solution (100 ml) and ethanol (100 ml) is refluxed for two hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in ice-water, and thereto is added conc. hydrochloric acid until the pH value of the mixture is adjusted to pH 1. The precipitated crystals are collected by filtration, washed with water, and washed with ethanol to give the desired compound (9.6 g).

Reference Examples 52-62

The corresponding starting compounds are treated in the same manner as in Reference Example 51 to give the compounds as listed in Table 12.

Table 12



Reference Ex.	W	Y	A
52	H	Et	Ph
53	H	H	Ph
54	Ph	Me	Ph
55	Me	Me	Ph-4-CF_3
56	Ph	Me	Ph-4-CF_3
57	H	-$CH_2CON(Me)_2$	Ph
58	H	-$CH_2CON(Et)_2$	Ph
59	H	-$CH_2CON(Bu)_2$	Ph
60	H	-$CH_2CON(Me)Ph$	Ph
61	H	-$CH_2CON(Et)Ph$	Ph
62	H	-$CH_2CON(Pr)Ph$	Ph

Reference Example 63

Preparation of 4-(N-benzyl-N-methylcarbamoylmethylamino)-2-phenyl-pyrimidine-5-carboxylic acid:

(1) A mixture of ethyl 4-chloro-2-phenylpyrimidine-5-carboxylate (21 g), glycine (6.6 g), trimethylamine (17.8 g) and ethanol (200 ml) is refluxed for four hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in water. To the mixture is added dropwise conc. hydrochloric acid under stirring at 0-5°C until the pH value of the mixture is adjusted to pH 4. The precipitates are collected by filtration, and washed with water to give crude N-(5-ethoxycarbonyl-2-phenyl-4-pyrimidinyl)glycine (24 g).

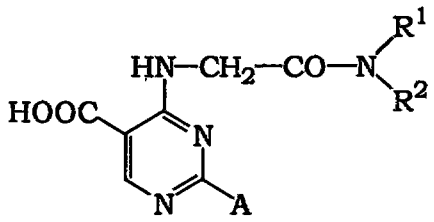
(2) A mixture of the above compound (6 g), N-methylbenzylamine (3.6 g), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium · hexafluorophosphate (hereinafter, referred to as BOP reagent, 13.3 g), triethylamine (3.0 g) and dimethylformamide (100 ml) is stirred at room temperature for one hour. The reaction mixture is concentrated under reduced pressure, and to the residue are added water and chloroform. The chloroform layer is separated, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform) to give crude ethyl 4-(N-benzyl-N-methylcarbamoylmethylamino)-2-phenyl-pyrimidine-5-carboxylate (7.8 g).

(3) A mixture of the above compound (7.8 g), 1N aqueous sodium hydroxide solution (100 ml) and ethanol (100 ml) is refluxed for two hours. The reaction mixture is concentrated under reduced pressure, and the residue is dissolved in ice-water. To the mixture is added conc. hydrochloric acid until the pH value of the mixture is adjusted to pH 1. The precipitated crystals are collected by filtration, washed with water, and washed with ethanol to give the desired compound (7.0 g).

Reference Examples 64-70

The corresponding starting compounds are treated in the same manner as in Reference Example 63 to give the compounds as listed in Table 13.

Table 13



Reference Ex.	R^1	R^2	A
64	Me	$-CH_2Ph$	Ph-4-Cl
65	Me	$-CH_2Ph$	Ph-4-F
66	Me	$-CH_2Ph$	Ph-4-OMe
67	Et	$-CH_2Ph$	Ph
68	Et	$-CH_2Ph$	Ph-4-Cl
69	Et	$-CH_2Ph$	Ph-4-F
70	Et	$-CH_2Ph$	Ph-4-OMe
71	Me	Bzl-4-F	Ph
72	Me	Bzl-3-F	Ph
73	Me	Bzl-2-F	Ph
74	Me	Bzl-4-Cl	Ph
75	Me	Bzl-4-OMe	Ph
76	Et	Bzl-4-F	Ph
77	Et	Bzl-3-F	Ph
78	Et	Bzl-2-F	Ph
79	Et	Bzl-4-Cl	Ph
80	Et	Bzl-4-OMe	Ph

Reference Example 81

Preparation of 4-ethylamino-5-nitro-2-phenylpyrimidine:

A mixture of 4-chloro-5-nitro-2-phenylpyrimidine (3 g), ethylamine hydrochloride (1.6 g), triethylamine (3.9 g) and isopropanol (60 ml) is refluxed for three hours. The reaction mixture is

concentrated under reduced pressure, and to the residue are added chloroform and water. The chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from isopropanol to give the desired compound (2.9 g).

M.p. 136-137°C.

Reference Example 82

Preparation of 4-methylamino-5-nitro-2-(4-trifluoromethylphenyl)-pyrimidine:

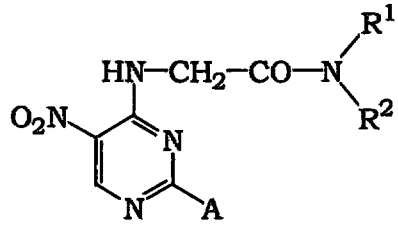
The corresponding starting compounds are treated in the same manner as in Reference Example 81, and the product thus obtained is further recrystallized from isopropanol to give the desired compound.

M.p. 170-172°C.

Reference Examples 83-92

The corresponding starting compounds are treated in the same manner as in Reference Example 81 to give the compounds as listed in Table 14.

Table 14



Reference Ex.	R^1	R^2	A	M.p. (°C)	Solvent for recrystal.
83	Pr	Pr	Ph	142-143	A
84	Pr	Pr	Ph-4-Cl	151-152	A
85	Me	Me	Ph-3-CF_3	205-207	IP
86	Me	Me	Ph-4-CF_3	225-226	A
87	Me	Ph	Ph	202-204	A
88	Me	Ph-3-Cl	Ph	147-148	A
89	Me	Ph-4-Cl	Ph	157-158	A
90	Me	Ph-4-OMe	Ph	209-210	A
91	Et	Ph	Ph	205-207	A
92	Me	Ph-4-OMe	Ph-4-Cl	172-173	A

Reference Example 93

Preparation of 6-chloro-4-methylamino-5-nitro-2-phenylpyrimidine:

The corresponding starting compounds are treated in the same manner as in Reference Example 81 to give the desired compound.

Example 1

Preparation of N-ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide:

To a mixture of about 60 % sodium hydride (oily) (1.4 g) and dimethylformamide (70 ml) is added 7,9-dihydro-9-methyl-2-pheny-8H-purin-8-one (7.0 g) in portions at 0-5°C, and the mixture is stirred at 0°C for one hour. To the mixture is added dropwise 2-bromo-N-ethyl-

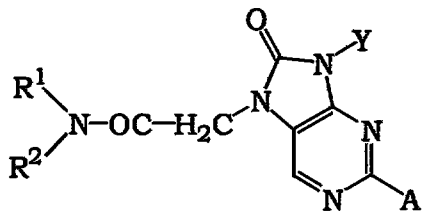
N-phenylacetamide (8.3 g) at the same temperature. After the addition, the mixture is stirred at room temperature for three hours. To the reaction mixture are added water and chloroform. The chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform) and recrystallized from ethanol to give the desired compound (10.3 g).

M.p. 240-242°C.

Examples 2-44

The corresponding starting compounds are treated in the same manner as in Example 1 to give the compounds as listed in Tables 15 and 16.

Table 15

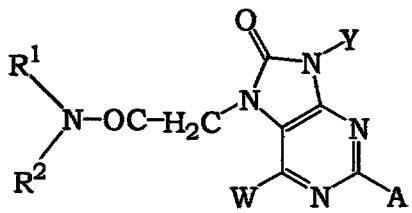


Ex.	R^1	R^2	Y	A	M.p. (°C)	Solvent for recrystal.
2	Me	Ph	Me	Ph	147-148	IP
3	Me	Ph	Me	Ph-3-Cl	188-189	A
4	Me	Ph	Me	Ph-4-Cl	188-190	A
5	Me	Ph	Me	Ph-4-F	169-170	A
6	Me	Ph	Me	Ph-4-OMe	176-178	A
7	Me	Ph	Me	Ph-4-NO_2	262-264	A-CF
8	Me	Ph	Et	Ph	160-161	A
9	Et	Ph	H	Ph	281-284	A
10	Et	Ph	Me	Ph-3-Cl	195-196	A
11	Et	Ph	Me	Ph-4-Cl	174-175	A
12	Et	Ph	Me	Ph-4-F	211-212	A
13	Et	Ph	Me	Ph-4-OMe	179-181	A
14	Et	Ph	Me	Ph-4-NO_2	231-232	A-CF
15	Et	Ph	Me	Ph-4-Me	197-198	A
16	Et	Ph	Et	Ph	165-167	A
17	Et	Ph	Pr	Ph	138-139	A
18	Et	Ph	-CH_2Ph	Ph	150-152	A
19	Et	Et	Me	Ph	207-209	A
20	Et	Et	Me	Ph-3-Cl	162-164	A
21	Et	Et	Me	Ph-4-Cl	157-159	A
22	Et	Et	Me	Ph-4-F	124-125	A
23	Et	Et	Me	Ph-4-OMe	137-139	A
24	Et	Et	Me	Ph-4-NO_2	238-240	A-CF
25	Et	Et	Et	Ph	148-150	A
26	Pr	Pr	Me	Ph	133-134	E

Table 15 (continued)

Ex.	R^1	R^2	Y	A	M.p. (°C)	Solvent for recrystal.
27	Pr	Pr	Me	Ph-3-Cl	133-135	A
28	Pr	Pr	Me	Ph-4-Cl	149-150	A
29	Pr	Pr	Me	Ph-4-F	154-155	A
30	Pr	Pr	Me	Ph-4-OMe	120-121	A
31	Pr	Pr	Me	Ph-4-NO_2	186-188	A-CF
32	Pr	Pr	Me	Ph-4-CF_3	150-151	A
33	Pr	Pr	Et	Ph	134-135	A
34	Et	Pr	Me	Ph	150-151	A
35	Me	Me	Me	Ph	204-206	A
36	Me	Me	Me	Ph-4-CF_3	200-202	A
37	Me	Ph	Me	3-Pyridyl	209-211	AN
38	Et	Ph	Me	3-Pyridyl	195-196	AN
39	Et	Ph	Me	2-Thienyl	236-238	A
40	Et	Ph	Me	3-Thienyl	226-228	A

Table 16



Ex.	W	R^1	R^2	Y	A	M.p. (°C)	Sol. for recrystal.
41	Ph	Et	Ph	Me	Ph	185-187	A
42	Me	Me	Me	Me	Ph-4-CF_3	217-219	A
43	Ph	Me	Me	Me	Ph-4-CF_3	234-235	IP
44	Ph-4-CF_3	Me	Me	Me	Ph	231-233	A

Example 45

Preparation of 6-chloro-N-ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide:

To a mixture of 6-chloro-7,9-dihydro-9-methyl-2-phenyl-8H-purin-8-one (1.6 g), potassium carbonate (1.0 g) and dimethylformamide (15 ml) is added 2-chloro-N-ethyl-N-phenylacetamide (1.4 g) at room temperature, and the mixture is stirred at the same temperature for two hours. To the reaction mixture is added water, and the precipitates are collected by filtration, washed with water, and purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give the desired compound (1.8 g).

M.p. 212-213°C.

Example 46

Preparation of N-ethyl-8,9-dihydro-6-methoxy-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide:

A mixture of 6-chloro-N-ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide (0.6 g) obtained in Example 45, a 28 % solution of sodium methoxide in methanol (0.3 g), methanol (20 ml) and 1,3-dimethyl-2-imidazolidinone (5 ml) is refluxed for four hours. The reaction mixture is concentrated under reduced pressure, and to the residue are added water and chloroform. The chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give the desired compound (0.3 g).

M.p. 173-175°C.

Example 47

Preparation of N-ethyl-8,9-dihydro-9-methyl-6-dimethylamino-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide:

A mixture of 6-chloro-N-ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide obtained in Example 45 (0.6 g), dimethylamine hydrochloride (0.2 g), triethylamine (0.4 g) and dimethylformamide (20 ml) is stirred at 100°C for four hours. The reaction mixture is concentrated under reduced pressure, and to the residue are added water and chloroform. The chloroform layer is separated, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from diisopropyl ether to give the desired compound (0.34 g).

M.p. 179-181°C.

Example 48

Preparation of N-benzyl-8,9-dihydro-9-methyl-N-methyl-8-oxo-2-phenyl-7H-purin-7-acetamide:

(1) A mixture of 7,9-dihydro-9-methyl-2-phenyl-8H-purin-8-one (22.6 g), ethyl chloroacetate (13.5 g), potassium carbonate (15.2 g) and dimethylformamide (250 ml) is stirred at room temperature for one hour. To the reaction mixture are added water and chloroform, and the chloroform layer is separated, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crude ethyl 8,9-dihydro-9-methyl-8-oxo-2-phenyl-7H-purin-7-acetate (26 g).

(2) A mixture of the above product (26 g), 1N aqueous sodium hydroxide solution (500 ml) and ethanol (500 ml) is refluxed for one

hour. The reaction mixture is concentrated under reduced pressure, and water is added to the residue. To the mixture is added dropwise conc. hydrochloric acid until the pH value of the mixture is adjusted to pH 1. The precipitates are collected by filtration, washed with water, and washed with ethanol to give crude 8,9-dihydro-9-methyl-8-oxo-2-phenyl-7H-purin-7-acetic acid (22 g).

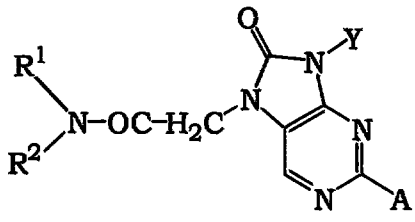
(3) A mixture of the above product (1.1 g), methylbenzylamine (0.7 g), BOP reagent (2.6 g), triethylamine (0.6 g) and dimethylformamide (30 ml) is stirred at room temperature for one hour. The reaction mixture is concentrated under reduced pressure, and water and chloroform are added to the residue. The chloroform layer is separated, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol and diisopropyl ether to give the desired compound (1.1 g).

M.p. 160-161°C.

Examples 49-65

The corresponding starting compounds are treated in the same manner as in Example 48 to give the compounds as listed in Table 17.

Table 17



Ex.	R^1	R^2	Y	A	M.p. (°C)	Solvent. for recrystal.
49	Me	$-CH_2Ph$	Me	Ph-4-Cl	210-211	A
50	Me	$-CH_2Ph$	Me	Ph-4-F	170-171	A
51	Me	$-CH_2Ph$	Me	Ph-4-OMe	205-206	A
52	Me	$-CH_2Ph$	Et	Ph	151-153	A
53	Me	$-CH_2Ph$	Pr	Ph	132-134	A
54	Et	$-CH_2Ph$	Me	Ph	112-115	A-IPE
55	Et	$-CH_2Ph$	Me	Ph-4-Cl	184-186	A
56	Et	$-CH_2Ph$	Me	Ph-4-F	155-157	A
57	Et	$-CH_2Ph$	Me	Ph-4-OMe	181-182	A
58	Et	$-CH_2Ph$	Et	Ph	133-134	A-IPE
59	Et	$-CH_2Ph$	Pr	Ph	114-116	A
60	Pr	Ph	Me	Ph	221-223	A
61	Pr	Ph	Et	Ph	168-170	A-IPE
62	Bu	Ph	Me	Ph	207-209	A
63	Bu	Bu	Me	Ph	138-139	A
64	Pent	Pent	Me	Ph	91-92	IPE
65	$-(CH_2)_5-$		Me	Ph	192-194	A

Example 66

Preparation of 8,9-dihydro-9-methyl-7-(2,6-dimethylmorpholin-4-yl-carbonylmethyl)-8-oxo-2-phenyl-7H-purine:

2,6-Dimethylmorpholine is treated in the same manner as in

Example 48-(3), and the product thus obtained is recrystallized from acetonitrile and diisopropyl ether to give the desired compound.

M.p. 160-161°C.

Example 67

Preparation of N-ethyl-N-phenyl-2-(8,9-dihydro-9-methyl-8-oxo-2-phenyl-7H-purin-7-yl)propanamide:

The same procedures as Example 48 are repeated except that ethyl 2-chloropropionate is used instead of ethyl chloroacetate in Example 48-(1), and N-ethylaniline is used instead of methyl benzylamine in Example 48-(3). The product thus obtained is recrystallized from ethanol to give the desired compound.

M.p. 150-151°C.

Example 68

Preparation of 8,9-dihydro-N-(2-hydroxyethyl)-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide:

(1) A mixture of 8,9-dihydro-9-methyl-8-oxo-2-phenyl-7H-purin-7-acetic acid (3 g) obtained in Example 48-(2), aniline (1.3 g), BOP reagent (5.1 g), triethylamine (1.2 g) and dimethylformamide (20 ml) is stirred at room temperature for two hours. To the reaction mixture is added water, and the precipitates are collected by filtration, and washed with water to give crude 8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide (3.5 g).

(2) To a mixture of about 60 % sodium hydride (oily) (0.3 g) and dimethylformamide (30 ml) is added the above product (2.5 g) in portions at 0-5°C, and the mixture is stirred at 0°C for one hour. To the mixture is added dropwise 2-bromoethyl acetate (2.2 g) at the same

temperature. After the addition, the mixture is stirred at room temperature for three hours. To the reaction mixture are added water and chloroform. The chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from isopropanol to give N-(2-acetoxy-ethyl)-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide (0.9 g).

M.p. 158-160°C.

(3) A mixture of the above product (0.9 g), potassium carbonate (0.3 g) and methanol (15 ml) is stirred at room temperature for three hours. To the reaction mixture is added water, and the precipitates are collected by filtration, washed with water, and recrystallized from methanol and acetonitrile to give the desired compound (0.05 g).

M.p. 231-233°C.

Example 69

Preparation of N-(4-fluorobenzyl)-8,9-dihydro-9-methyl-N-methyl-8-oxo-2-phenyl-7H-purin-7-acetamide:

(1) A mixture of 8,9-dihydro-9-methyl-8-oxo-2-phenyl-7H-purin-7-acetic acid (9.1 g) obtained in Example 48-(2), methylamine hydrochloride (3.2 g), BOP reagent (21.2 g), triethylamine (9.7 g), and dimethylformamide (100 ml) is stirred at room temperature for two hours. Water is added to the reaction mixture, and the precipitates are collected by filtration, and washed with water to give crude 8,9-dihydro-9-methyl-N-methyl-8-oxo-2-phenyl-7H-purin-7-acetamide (8.1 g).

(2) To a mixture of about 60 % sodium hydride (oily) (0.2 g) and

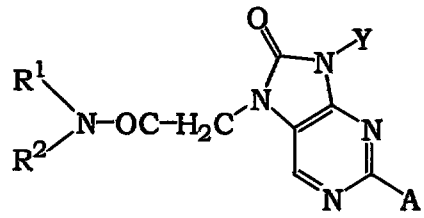
dimethylformamide (30 ml) is added the above product (1.2 g) in portions at 0-5°C, and the mixture is stirred at 0°C for one hour. To the mixture is added dropwise 4-fluorobenzyl bromide (1.0 g) at the same temperature. After the addition, the mixture is stirred at room temperature for three hours. Water and chloroform are added to the reaction mixture, and the chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give the desired compound (0.6 g).

M.p. 197-199°C.

Examples 70-78

The corresponding starting compounds are treated in the same manner as in Example 69 to give the compounds as listed in Table 18.

Table 18



Ex.	R^1	R^2	Y	A	M.p. (°C)	Solvent for recrystal.
70	Me	Bzl-3-F*	Me	Ph	163-164	A
71	Me	Bzl-2-F	Me	Ph	198-199	A
72	Me	Bzl-4-Cl	Me	Ph	183-184	A
73	Me	Bzl-4-OMe	Me	Ph	174-176	A
74	Et	Bzl-4-F	Me	Ph	166-167	A
75	Et	Bzl-3-F	Me	Ph	144-145	A
76	Et	Bzl-2-F	Me	Ph	164-165	A
77	Et	Bzl-4-Cl	Me	Ph	198-199	A
78	Et	Bzl-4-OMe	Me	Ph	155-156	A

*: In the above Table, Bzl-3-F means 3-fluorobenzyl group.

Example 79

Preparation of 7,8-dihydro-8-oxo-2-phenyl-N,N-dipropyl-9H-purin-9-acetamide:

To a mixture of 2-phenyl-4-(N,N-dipropylcarbamoylmethyl-amino)pyrimidine-5-carboxylic acid (10 g) and dimethylformamide (70 ml) is added triethylamine (2.8 g) at room temperature, and the mixture is stirred for 10 minutes, and thereto is added diphenylphosphoryl azide (7.7 g) at the same temperature. The reaction mixture is stirred at 100°C for two hours, and concentrated under reduced pressure. The residue is poured into ice-water, and the precipitates are collected by filtration, washed with water, and recrystallized from ethanol to give the

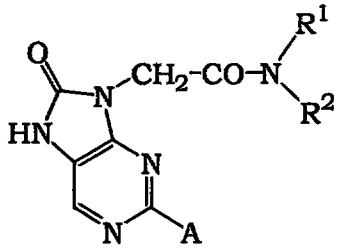
desired compound (7 g).

M.p. 190-191°C.

Examples 80-96

The corresponding starting compounds are treated in the same manner as in Example 79 to give the compounds as listed in Table 19.

Table 19



Ex.	R^1	R^2	A	M.p. (°C)	Solvent for recrystal.
80	Pr	Pr	Ph-3-Cl	172-174	A
81	Pr	Pr	Ph-4-F	213-215	A
82	Pr	Pr	Ph-4-OMe	159-160	A
83	Pr	Pr	Ph-4-NO_2	256-258	A
84	Me	Ph	3-Pyridyl	268-270	CF-AN
85	Et	Et	Ph	222-224	A-CF
86	Me	Me	Ph	>300	A
87	Me	-CH_2Ph	Ph	261-263	A
88	Me	-CH_2Ph	Ph-4-Cl	289-290	A
89	Me	-CH_2Ph	Ph-4-F	286-288	A
90	Me	-CH_2Ph	Ph-4-OMe	240-241	A
91	Et	-CH_2Ph	Ph	212-214	A
92	Et	-CH_2Ph	Ph-4-Cl	264-266	A
93	Et	-CH_2Ph	Ph-4-F	236-238	A
94	Et	-CH_2Ph	Ph-4-OMe	216-218	A
95	Bu	Bu	Ph	196-198	A-IPE
96	Pr	Ph	Ph	258-260	A

Example 97

Preparation of 2-(4-chlorophenyl)-7,8-dihydro-8-oxo-N,N-dipropyl-9H-purin-9-acetamide:

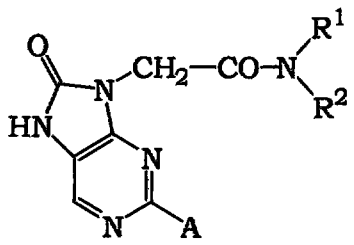
A mixture of 2-[2-(4-chlorophenyl)-5-nitro-4-pyrimidinylamino]-N,N-dipropylacetamide (9 g), platinum (IV) oxide (1 g) and ethanol (150 ml) is stirred under hydrogen atmosphere for four hours, and the reaction mixture is filtered. The filtrate is concentrated under reduced pressure, and to the resulting residue is added urea (2.1 g). The mixture is stirred at 200°C for two hours. After cooling, water is added to the reaction mixture, and the precipitates are collected by filtration, washed with water, and recrystallized from ethanol to give the desired compound (7 g).

M.p. 177-178°C.

Examples 98-105

The corresponding starting compounds are treated in the same manner as in Example 97 to give the compounds as listed in Table 20.

Table 20



Ex.	R^1	R^2	A	M.p. (°C)	Solvent for recrystal.
98	Me	Ph	Ph	286-287	M
99	Me	Ph-3-Cl	Ph	234-236	M
100	Me	Ph-4-Cl	Ph	244-246	M
101	Me	Ph-4-OMe	Ph	238-240	A
102	Me	Ph-4-OMe	Ph-4-Cl	277-280	A
103	Et	Ph	Ph	237-238	A
104	Me	Me	Ph-4-CF_3	>300	A
105	Me	Me	Ph-3-CF_3	254-255	A

Example 106

Preparation of 7,8-dihydro-7-methyl-8-oxo-2-phenyl-N,N-dipropyl-9H-purin-9-acetamide:

To a mixture of about 60 % sodium hydride (oily) (0.8 g) and dimethylformamide (50 ml) is added 7,8-dihydro-8-oxo-2-phenyl-N,N-dipropyl-9H-purin-9-acetamide (6 g) obtained in Example 79 in portions at 0-5°C, and the mixture is stirred at 0°C for one hour. To the mixture is added dropwise methyl iodide (2.9 g) at the same temperature. After the addition, the mixture is stirred at room temperature for two hours. To the reaction mixture are added water and chloroform, and the chloroform layer is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

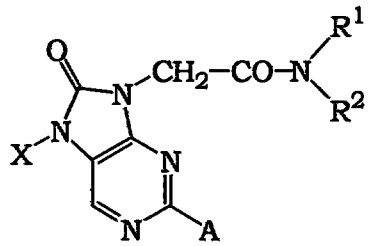
The residue is purified by silica gel column chromatography (eluent; chloroform), and recrystallized from ethanol to give the desired compound (6 g).

M.p. 156-157°C.

Examples 107-172

The corresponding starting compounds are treated in the same manner as in Example 106 to give the compounds as listed in Table 21.

Table 21



Ex.	R^1	R^2	X	A	M.p. (°C)	Solvent for recrystal.
107	Pr	Pr	Et	Ph	98-99	E
108	Pr	Pr	$-CH_2Ph$	Ph	130-131	IP
109*	Pr	Pr	$-CONH_2$	Ph	183-185	M
110	Pr	Pr	$-CON(Me)_2$	Ph	128-130	E
111	Pr	Pr	Me	Ph-3-Cl	166-167	A
112	Pr	Pr	Me	Ph-4-Cl	135-137	IP
113	Pr	Pr	Me	Ph-4-F	140-141	A
114	Pr	Pr	Me	Ph-4-OMe	157-158	A
115	Pr	Pr	Me	Ph-4-NO_2	218-219	A
116	Pr	Pr	Et	Ph-4-Cl	158-159	IP

*: 1/4 hydrate

Table 21 (continued)

Ex.	R^1	R^2	X	A	M.p. (°C)	Solvent for recrystal.
117	Pr	Pr	Et	Ph-4-F	134-136	A
118	Pr	Pr	Et	Ph-4-OMe	122-123	A
119	Pr	Pr	Et	Ph-4-NO_2	179-180	A
120	Pr	Pr	Pr	Ph	125-127	A-IPE
121	Pr	Pr	Pr	Ph-4-Cl	107-108	IP
122	Pr	Pr	Bu	Ph	129-130	A-IPE
123	Pr	Pr	Pent	Ph	117-118	A-IPE
124	Et	Et	Me	Ph	204-206	A
125	Et	Et	Et	Ph	198-200	A
126	Et	Et	Pr	Ph	141-143	A-IPE
127	Me	Me	Me	Ph	262-264	A-CF
128	Me	Me	Et	Ph	187-189	A
129	Me	Me	Me	Ph-4-CF_3	256-258	A
130	Me	Me	Et	Ph-4-CF_3	230-232	A
131	Me	Me	-$CONH_2$	Ph-4-CF_3	>300	M
132	Me	Me	Me	Ph-3-CF_3	209-210	A
133	Me	Me	Et	Ph-3-CF_3	173-174	IP
134	Bu	Bu	Me	Ph	192-193	A
135	Bu	Bu	Et	Ph	135-136	A-IPE
136	Me	-CH_2Ph	Me	Ph	169-170	A-IPE
137	Me	-CH_2Ph	Me	Ph-4-Cl	241-242	A-CF
138	Me	-CH_2Ph	Me	Ph-4-F	192-193	A
139	Me	-CH_2Ph	Me	Ph-4-OMe	197-199	A
140	Me	-CH_2Ph	Et	Ph	147-149	A-IPE
141	Me	-CH_2Ph	Et	Ph-4-Cl	197-198	A
142	Me	-CH_2Ph	Et	Ph-4-F	174-175	A
143	Me	-CH_2Ph	Et	Ph-4-OMe	161-162	A
144	Me	-CH_2Ph	Pr	Ph	155-157	A
145	Me	-CH_2Ph	-$CON(Me)_2$	Ph	195-196	A
146	Et	-CH_2Ph	Me	Ph	163-164	A
147	Et	-CH_2Ph	Me	Ph-4-Cl	172-173	A
148	Et	-CH_2Ph	Me	Ph-4-F	169-170	A
149	Et	-CH_2Ph	Me	Ph-4-OMe	157-158	A

Table 21 (continued)

Ex.	R^1	R^2	X	A	M.p. (°C)	Solvent for recrystal.
150	Et	$-CH_2Ph$	Et	Ph	134-136	A-IPE
151	Et	$-CH_2Ph$	Et	Ph-4-Cl	157-158	A
152	Et	$-CH_2Ph$	Et	Ph-4-F	135-136	A-IPE
153	Et	$-CH_2Ph$	Et	Ph-4-OMe	129-131	IPE
154	Et	$-CH_2Ph$	Pr	Ph	126-127	A-IPE
155	Et	$-CH_2Ph$	$-CON(Me)_2$	Ph	152-153	A-IPE
156*	Me	Ph	Me	Ph	202-203	A
157*	Me	Ph	Et	Ph	170-171	A
158	Me	Ph	Pr	Ph	183-185	A
159	Me	Ph	$-CH_2Ph$	Ph	194-195	A
160	Me	Ph	$-CON(Me)_2$	Ph	204-205	A
161	Me	Ph-3-Cl	Et	Ph	205-207	A
162	Me	Ph-4-Cl	Et	Ph	173-175	A
163	Me	Ph-4-OMe	Me	Ph	172-174	IP
164	Me	Ph-4-OMe	Et	Ph	142-144	IP
165	Me	Ph-4-OMe	Et	Ph-4-Cl	184-186	IP
166	Et	Ph	Me	Ph	180-181	IP
167	Et	Ph	Et	Ph	154-155	A
168	Et	Ph	Pr	Ph	140-142	A
169	Pr	Ph	Me	Ph	174-176	A
170	Pr	Ph	Et	Ph	151-152	A
171	Me	Ph	Me	3-Pyridyl	216-217	AN
172	Me	Ph	Et	3-Pyridyl	199-200	AN

*: 1/4 hydrate

Example 173

Preparation of 8,9-dihydro-N-(4-methoxyphenyl)-9-methyl-N-ethyl-8-oxo-2-phenyl-7H-purin-7-acetamide:

The corresponding starting compounds are treated in the same manner as in Example 48, and the resulting product is recrystallized

from ethanol to give the desired compound.

M.p. 208-209°C.

Example 174

Preparation of 8,9-dihydro-N-(4-hydroxyphenyl)-9-methyl-N-ethyl-8-oxo-2-phenyl-7H-purin-7-acetamide:

To a mixture of 8,9-dihydro-N-(4-methoxyphenyl)-9-methyl-N-ethyl-8-oxo-2-phenyl-7H-purin-7-acetamide (0.83 g) obtained in Example 173 and dichloromethane (10 ml) is added a 1M solution of boron tribromide in dichloromethane (4 ml) at 0°C, and the mixture is stirred at room temperature for five days. To the reaction mixture is added water, and the precipitates are collected by filtration, washed with water, and recrystallized from ethanol and diisopropyl ether to give the desired compound (0.38 g).

M.p. 254-256°C.

Example 175

Preparation of N-benzyl-N-ethyl-7,8-dihydro-9-methyl-8-oxo-2-phenyl-9H-purin-9-acetamide hydrochloride:

To a mixture of N-benzyl-N-ethyl-7,8-dihydro-9-methyl-8-oxo-2-phenyl-9H-purin-9-acetamide (0.8 g) obtained in Example 146 and ethanol (15 ml) is added 30 % hydrochloric acid in ethanol (15 ml) at 80°C, and the mixture is stirred for 30 minutes. The reaction mixture is cooled to room temperature, and the precipitates are collected by filtration, and washed with ethanol to give the desired compound (0.85 g).

M.p. 169-172°C.

Example 176

Preparation of N-ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide hydrochloride:

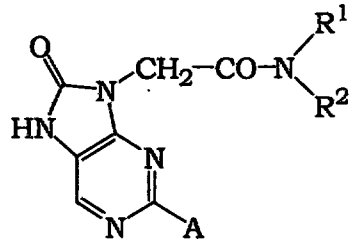
Using N-ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide obtained in Example 1, the same procedures as Example 175 are repeated to give the desired compound.

M.p. 248-249°C.

Examples 177-186

The corresponding starting compounds are treated in the same manner as in Example 79 to give the compounds as listed in Table 22.

Table 22

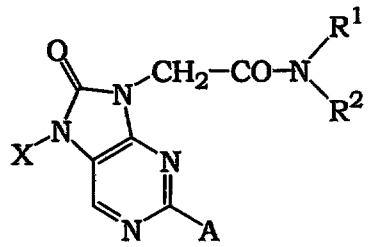


Ex.	R^1	R^2	A	M.p. (°C)	Solvent for recrystal.
177	Me	Bzl-4-F	Ph	269-270	A
178	Me	Bzl-3-F	Ph	256-258	A
179	Me	Bzl-2-F	Ph	234-235	A-IPE
180	Me	Bzl-4-Cl	Ph	276-277	A-CF
181	Me	Bzl-4-OMe	Ph	245-246	A-IPE
182	Et	Bzl-4-F	Ph	256-258	A-CF
183	Et	Bzl-3-F	Ph	217-219	A-IPE
184	Et	Bzl-2-F	Ph	200-203	A-IPE
185	Et	Bzl-4-Cl	Ph	234-236	A-CF
186	Et	Bzl-4-OMe	Ph	177-178	A-IPE

Examples 187-206

The corresponding starting compounds are treated in the same manner as in Example 106 to give the compounds as listed in Table 23.

Table 23



Ex.	R^1	R^2	X	A	M.p. (°C)	Solvent for recrystal.
187	Me	Bzl-4-F	Me	Ph	207-208	A
188	Me	Bzl-4-F	Et	Ph	195-196	A-IPE
189	Me	Bzl-3-F	Me	Ph	173-175	A
190	Me	Bzl-3-F	Et	Ph	146-147	A-IPE
191	Me	Bzl-2-F	Me	Ph	164-166	A-IPE
192	Me	Bzl-2-F	Et	Ph	159-161	A-IPE
193	Me	Bzl-4-Cl	Me	Ph	244-245	A-CF
194	Me	Bzl-4-Cl	Et	Ph	203-205	A
195	Me	Bzl-4-OMe	Me	Ph	205-207	A
196	Me	Bzl-4-OMe	Et	Ph	183-185	A-IPE
197	Et	Bzl-4-F	Me	Ph	205-206	A
198	Et	Bzl-4-F	Et	Ph	155-156	A-IPE
199	Et	Bzl-3-F	Me	Ph	173-174	A-IPE
200	Et	Bzl-3-F	Et	Ph	147-148	A-IPE
201	Et	Bzl-2-F	Me	Ph	180-181	A
202	Et	Bzl-2-F	Et	Ph	159-160	A-IPE
203	Et	Bzl-4-Cl	Me	Ph	216-217	A
204	Et	Bzl-4-Cl	Et	Ph	141-142	A-IPE
205	Et	Bzl-4-OMe	Me	Ph	173-175	A
206	Et	Bzl-4-OMe	Et	Ph	153-154	A

The intermediates represented by the formula (II) are exemplified as follows.

Example 207

Preparation of 7,9-dihydro-9-methyl-2-phenyl-8H-purin-8-one:

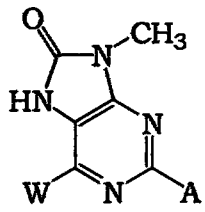
To a mixture of 4-methylamino-2-phenylpyrimidine-5-carboxylic acid (7 g) and dimethylformamide (50 ml) is added triethylamine (3.1 g) at room temperature, and the mixture is stirred for 10 minutes, and thereto is added diphenylphosphoryl azide (8.4 g) at the same temperature. The reaction mixture is stirred at 120°C for four hours, and concentrated under reduced pressure. The residue is poured into ice-water, and the precipitates are collected by filtration, washed with water, washed with ethanol, and recrystallized from chloroform to give the desired compound (5 g).

M.p. 286-289°C.

Examples 208-220

The corresponding starting compounds are treated in the same manner as in Example 207 to give the compounds as listed in Table 24.

Table 24



Ex.	W	A	M.p. (°C)	Solvent for recrystal.
208	H	Ph-3-Cl	296-298	CF
209	H	Ph-4-Cl	>300	CF
210	H	Ph-4-F	>300	CF
211	H	Ph-4-OMe	>300	CF
212	H	Ph-4-NO_2	>300	CF
213	H	Ph-4-Me	283-285	CF
214	H	3-Pyridyl	293-294	DMF
215	H	2-Thienyl	>300	CF
216	H	3-Thienyl	287-288	CF
217	Ph	Ph	>300	CF
218	Ph-4-CF_3	Ph	>300	M
219	Me	Ph-4-CF_3	>300	M
220	Ph	Ph-4-CF_3	>300	M

Example 221

Preparation of 7,9-dihydro-9-benzyl-2-phenyl-8H-purin-8-one:

The corresponding starting compounds are treated in the same manner as in Example 207 to give the desired compound.

M.p. 286-287°C (recrystallized from chloroform).

Example 222

Preparation of 7,9-dihydro-2-phenyl-9-propyl-8H-purin-8-one:

The corresponding starting compounds are treated in the same manner as in Example 207 to give the desired compound.

M.p. 263-264°C (recrystallized from ethanol).

Example 223

Preparation of 9-ethyl-7,9-dihydro-2-phenyl-8H-purin-8-one:

A mixture of 4-ethylamino-5-nitro-2-phenylpyrimidine (2.7 g), palladium-carbon (0.3 g), and ethanol (50 ml) is stirred at room temperature under hydrogen atmosphere for five hours, and the reaction mixture is filtered. The filtrate is concentrated under reduced pressure, and to the resulting residue is added urea (1.4 g). The mixture is stirred at 200°C for two hours. After cooling, water is added to the reaction mixture, and the precipitates are collected by filtration, washed with water, and washed with ethanol to give the desired compound (2.4 g).

M.p. 268-270°C (recrystallized from chloroform).

Example 224

Preparation of 7,9-dihydro-9-methyl-2-(4-trifluoromethylphenyl)-8H-purin-8-one:

The corresponding starting compounds are treated in the same manner as in Example 223, and the product is further recrystallized from isopropanol to give the desired compound.

M.p. 248-250°C.

Example 225

Preparation of 6-chloro-7,9-dihydro-9-methyl-2-phenyl-8H-purin-8-one:

The corresponding starting compounds are treated in the same manner as in Example 223 to give the desired compound as a solid.

Preparation 1: Preparation of tablets:

N-Ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide	1 g
Lactose	84 g
Corn starch	30 g
Crystalline cellulose	25 g
Hydroxypropyl cellulose	3 g

The above components are mixed and kneaded in a conventional manner, and the mixture is granulated. To the resultant are added light anhydrous silicic acid (0.7 g) and magnesium stearate (1.3 g), and the mixture is further tabletted to give 1,000 tablets (each 145 mg).

Preparation 2: Preparation of capsules

N-Ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide	2 g
Lactose	165 g
Corn starch	25 g
Hydroxypropyl cellulose	3.5 g
Light anhydrous silicic acid	1.8 g
Magnesium stearate	2.7 g

The above components are mixed and kneaded in a conventional manner, and the mixture is granulated, and each 200 mg of the resultant is packed into a capsule to give 1,000 capsules.

Preparation 3: Preparation of powder

N-Ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide	10 g

Lactose	960 g
Hydroxypropyl cellulose	25 g
Light anhydrous silicic acid	5 g

The above components are mixed by a conventional manner to give a powder preparation.

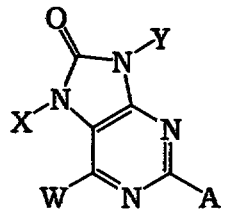
INDUSTRIAL APPLICABILITY

As explained above, the present compounds of the formula (I) or a pharmaceutically acceptable acid addition salt thereof show a selective and remarkable affinity for the peripheral-type $BZ\omega_3$-receptor as well as show excellent pharmacological activities such as anti-anxiety activity, etc. in animal tests, and hence, they are useful in the prophylaxis or treatment of central nervous disorders such as anxiety-related diseases (neurosis, somatoform disorders, anxiety disorders, and others), depression, epilepsy, etc., or circulatory organs disorders such as angina pectoris, hypertension, etc. Besides, the compounds of the formula (II) of the present invention are useful as an intermediate for preparing the compound of the formula (I) wherein X is a group of the formula (Q).



CLAIMS

1. A 2-aryl-8-oxodihydropurine derivative of the following formula (I):



(I)

wherein W is a hydrogen atom, a lower alkyl group, a halogen atom, a lower alkoxy group, an amino group, a mono- or di-lower alkylamino group, or a substituted or unsubstituted phenyl group;

X is a hydrogen atom, a lower alkyl group, a cycloalkyl-lower alkyl group, a substituted or unsubstituted phenyl-lower alkyl group, a lower alkenyl group, a carbamoyl group, a di-lower alkylcarbamoyl group, or a group of the formula (Q):

$$-CH(R^3)CON(R^1)(R^2) \qquad (Q)$$

(wherein R^1 is a lower alkyl group, a lower alkenyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, or a hydroxy-lower alkyl group, R^2 is a lower alkyl group, a cycloalkyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted phenyl-lower alkyl group, or a substituted or unsubstituted heteroaryl group, or R^1 and R^2 may combine together with the adjacent nitrogen atom to form a piperidine ring, a pyrrolidine ring, a morpholine ring or a piperazine ring, and these rings may optionally be substituted by one or two lower alkyl groups, and R^3 is a hydrogen atom, a lower alkyl group, or a

hydroxy-lower alkyl group);

Y is a hydrogen atom, a lower alkyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, a lower alkenyl group, a substituted or unsubstituted phenyl-lower alkyl group, or a group of the formula (Q):

$$-CH(R^3)CON(R^1)(R^2) \qquad (Q)$$

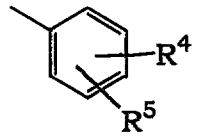
(wherein R^1, R^2 and R^3 are the same as defined above); and

A is a substituted or unsubstituted phenyl group, or a substituted or unsubstituted heteroaryl group;

provided that when one of X and Y of the above formula (I) is the group of the formula (Q), then the other is the same groups for X or Y as described above except for the group of the formula (Q),

or a pharmaceutically acceptable acid addition salt thereof.

2. The compound according to claim 1, wherein A is a group of the formula (A'):



[A']

(wherein R^4 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy group, an amino group, a mono- or di-lower alkylamino group, a cyano group, or a nitro group, and R^5 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower akoxy group, or a hydroxy group),

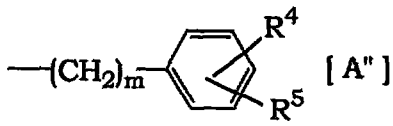
a pyridyl group, a thienyl group or a furyl group.

3. The compound according to any one of claims 1 and 2, wherein

(a) X is a group of the formula (Qx):

$$-CH(R^{31})CON(R^{11})(R^{21}) \qquad (Qx)$$

wherein R^{11} is a lower alkyl group, and R^{21} is a lower alkyl group or a group of the formula (A"):



[A"]

(wherein R^4 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, a trifluoromethyl group, a hydroxy group, an amino group, a mono- or di-lower alkylamino group, a cyano group, or a nitro group, R^5 is a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group, or a hydroxy group, and m is 0, 1 or 2), or

R^{11} and R^{21} may combine together with the adjacent nitrogen atom to form a piperidine ring, a pyrrolidine ring, a morpholine ring, or a piperazine ring, and these rings may optionally be substituted by one or two lower alkyl groups, and R^{31} is a hydrogen atom, a lower alkyl group, or a hydroxy-lower alkyl group,

Y is a hydrogen atom or a lower alkyl group, or

(b) X is a hydrogen atom, a lower alkyl group, or a carbamoyl group,

Y is a group of the formula (Qy):

$$-CH(R^{31})CON(R^{11})(R^{21}) \qquad (Qy)$$

wherein R^{11}, R^{21}, and R^{31} are the same as defined above.

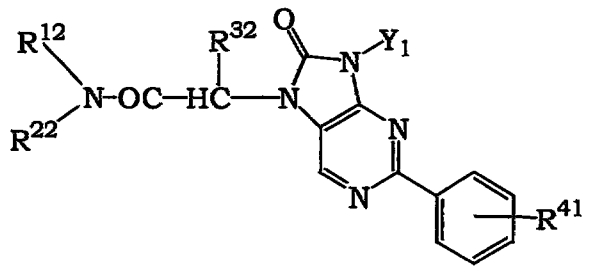
4. The compound according to claim 3, wherein

(a) X is the group of the above formula (Qx) (wherein R^{11} is a

methyl group, an ethyl group, a propyl group, an isopropyl group, or a butyl group, R^{21} is an ethyl group, a propyl group, an isopropyl group, a butyl group, a phenyl group, or a phenyl group being substituted by a halogen, a methoxy, a trifluoromethyl, or a hydroxy, a benzyl group, or a benzyl group being substituted by a halogen, a methoxy, a trifluoromethyl, or a hydroxy, and R^{31} is the same as defined in claim 3), and Y is a hydrogen atom, a methyl group, or an ethyl group, or

(b) X is a hydrogen atom, a methyl group, an ethyl group, a propyl group, an isopropyl group, or a butyl group, and Y is the group of the above formula (Qy) (wherein R^{11} is a methyl group, an ethyl group, a propyl group, an isopropyl group, or a butyl group, R^{21} is an ethyl group, a propyl group, an isopropyl group, a butyl group, a phenyl group, a phenyl group being substituted by a halogen, a methoxy, a trifluoromethyl, or a hydroxy, a benzyl group, or a benzyl group being substituted by a halogen, a methoxy, a trifluoromethyl, or a hydroxy, and R^{31} is the same as defined in claim 3).

5. A 2-aryl-8-oxodihydropurine derivative of the formula (Ia):



(Ia)

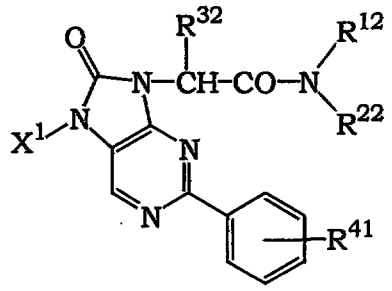
wherein R^{12} and R^{22} are the same or different, and each an ethyl group, a propyl group, or a butyl group, or R^{12} is a methyl group, an ethyl group, or a propyl group, R^{22} is a phenyl group, a halogenophenyl group,

a methoxyphenyl group, a benzyl group, a halogenobenzyl group, or a methoxybenzyl group, R^{32} is a hydrogen atom, a methyl group, or an ethyl group, Y^1 is a hydrogen atom, a methyl group, or an ethyl group, and R^{41} is a hydrogen atom, a halogen atom, a methyl group, a methoxy group, a nitro group, or a trifluoromethyl group,

or a pharmaceutically acceptable acid addition salt thereof.

6. The compound according to claim 5, wherein R^{32} is a hydrogen atom.

7. A 2-aryl-8-oxodihydropurine derivative of the formula (Ib):



(Ib)

wherein X^1 is a hydrogen atom, a methyl group, an ethyl group, or a propyl group, R^{12} and R^{22} are the same or different, and each an ethyl group, a propyl group, or a butyl group, or R^{12} is a methyl group, an ethyl group, or a propyl group, and R^{22} is a phenyl group, a halogenophenyl group, a methoxyphenyl group, a benzyl group, a halogenobenzyl group, or a methoxybenzyl group, R^{32} is a hydrogen atom, a methyl group, or an ethyl group, and R^{41} is a hydrogen atom, a halogen atom, a methyl group, a methoxy group, a nitro group, or a trifluoromethyl group,

or a pharmaceutically acceptable acid addition salt thereof.

8. The compound according to claim 7, wherein R^{32} is a

hydrogen atom.

9. A compound that is selected from the following compounds:

8,9-dihydro-9-methyl-N-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide;

8,9-dihydro-2-(4-fluorophenyl)-9-methyl-N-methyl-8-oxo-N-phenyl-7H-purin-7-acetamide;

N-ethyl-8,9-dihydro-2-(4-fluorophenyl)-9-methyl-8-oxo-N-phenyl-7H-purin-7-acetamide;

7,8-dihydro-7-methyl-8-oxo-2-phenyl-N,N-dipropyl-9H-purin-9-acetamide;

7-ethyl-7,8-dihydro-8-oxo-2-phenyl-N,N-dipropyl-9H-purin-9-acetamide;

N-benzyl-N-ethyl-7,8-dihydro-7-methyl-8-oxo-2-phenyl-9H-purin-9-acetamide;

N-benzyl-7,8-dihydro-N-methyl-7-methyl-8-oxo-2-phenyl-9H-purin-9-acetamide;

N-benzyl-N-ethyl-7,8-dihydro-7-methyl-8-oxo-2-(4-chloro-phenyl)-9H-purin-9-acetamide; and

N-benzyl-7,8-dihydro-N-methyl-7-methyl-8-oxo-2-(4-chloro-phenyl)-9H-purin-9-acetamide,

or a pharmaceutically acceptable acid addition salt thereof.

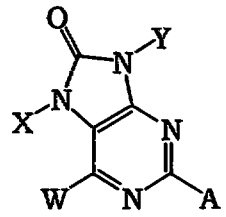
10. N-Ethyl-8,9-dihydro-9-methyl-8-oxo-2-phenyl-N-phenyl-7H-purin-7-acetamide,

or a pharmaceutically acceptable acid addition salt thereof.

11. A process for preparing a 2-aryl-8-oxodihydropurine

This Sheet Has Been Replaced

derivative of the formula (I):



(I)

wherein W is a hydrogen atom, a lower alkyl group, a halogen atom, a lower alkoxy group, an amino group, a mono- or di-lower alkylamino group, or a substituted or unsubstituted phenyl group;

X is a hydrogen atom, a lower alkyl group, a cycloalkyl-lower alkyl group, a substituted or unsubstituted phenyl-lower alkyl group, a lower alkenyl group, a carbamoyl group, a di-lower alkylcarbamoyl group, or a group of the formula (Q):

$$-CH(R^3)CON(R^1)(R^2) \qquad (Q)$$

(wherein R^1 is a lower alkyl group, a lower alkenyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, or a hydroxy-lower alkyl group, R^2 is a lower alkyl group, a cycloalkyl group, a substituted or unsubstituted phenyl group, a substituted or unsubstituted phenyl-lower alkyl group, or a substituted or unsubstituted heteroaryl group, or R^1 and R^2 may combine together with the adjacent nitrogen atom to form a piperidine ring, a pyrrolidine ring, a morpholine ring or a piperazine ring, and these rings may optionally be substituted by one or two lower alkyl groups, and R^3 is a hydrogen atom, a lower alkyl group, or a hydroxy-lower alkyl group);

Y is a hydrogen atom, a lower alkyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, a lower alkenyl group, a substituted or

unsubstituted phenyl-lower alkyl group, or a group of the formula (Q):

$$-CH(R^3)CON(R^1)(R^2) \qquad (Q)$$

(wherein R^1, R^2 and R^3 are the same as defined above); and

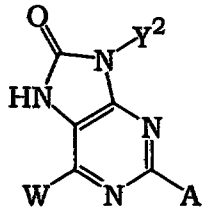
A is a substituted or unsubstituted phenyl group, or a substituted or unsubstituted heteroaryl group;

provided that when one of X and Y of the above formula (I) is the group of the formula (Q), then the other is the same groups for X or Y as described above except for the group of the formula (Q),

or a pharmaceutically acceptable acid addition salt thereof,

which comprises the following process (a), (b), (c), (d), or (e):

(a): when the compound (I) is a compound of the formula (I) wherein Y is a hydrogen atom, a lower alkyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, a lower alkenyl group, or a substituted or unsubstituted phenyl-lower alkyl group, reacting a compound of the formula (II):



(II)

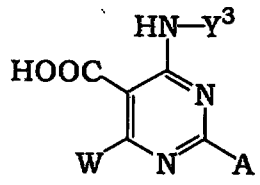
wherein Y^2 is a hydrogen atom, a lower alkyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, a lower alkenyl group, or a substituted or unsubstituted phenyl-lower alkyl group, and A and W are the same as defined above, with a compound of the formula (III):

$$Z\text{-}CH(R^3)\text{-}CON(R^1)(R^2) \qquad (III)$$

wherein Z is a leaving atom or a leaving group, and R^1, R^2 and R^3 are the same as defined above, and if necessary, followed by removing the

protecting groups from the product;

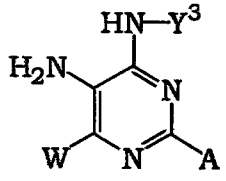
(b) when the compound (I) is a compound of the formula (I) wherein X is a hydrogen atom, and Y is a group of the formula (Q), reacting a compound of the formula (IV):



(IV)

wherein Y^3 is a group of the above formula (Q), and A and W are the same as defined above, with an azide compound, and if necessary, followed by removing the protecting groups from the product;

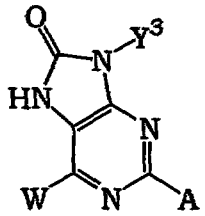
(c) when the compound (I) is a compound of the formula (I) wherein X is a hydrogen atom, and Y is a group of the formula (Q), reacting a compound of the formula (V):



(V)

wherein A, W and Y^3 are the same as defined above, with urea, a carbonyldiimidazole or a diethyl carbonate, and if necessary, followed by removing the protecting groups from the product;

(d) when the compound (I) is a compound of the formula (I) wherein X is a hydrogen atom, or the groups other than a group of the formula (Q), and Y is a group of the formula (Q), reacting a compound of the formula (VI):



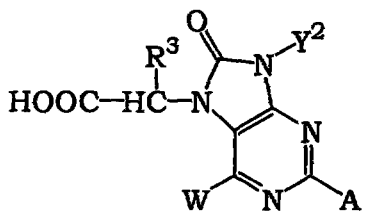
(VI)

wherein A, W and Y^3 are the same as defined above, with a compound of the formula (VII):

$$Z\text{-}X^2 \qquad \text{(VII)}$$

wherein X^2 is a hydrogen atom or the same groups for X as defined above except for a group of the formula (Q), and Z is the same as defined above, and if necessary, followed by removing the protecting groups from the product; and

(e) when the compound (I) is a compound of the formula (I) wherein X is a group of the formula (Q), reacting a compound of the formula (VIII):



(VIII)

wherein A, R^3, W and Y^2 are the same as defined above, or a reactive derivative thereof, with a compound of the formula (IX):

$$HN(R^{13})(R^{23}) \qquad \text{(IX)}$$

wherein R^{13} and R^{23} are each a hydrogen atom or the same groups for R^1 and R^2 as defined above, respectively, and when one of R^{13} and R^{23} is a hydrogen atom, then further reacting the product with a compound of the formula (X):

$$R^{24}\text{-}Z \qquad \text{(X)}$$

* C L M S *

or the formula (XI):

$$R^{14}\text{-}Z \qquad \text{(XI)}$$

wherein R^{24} is a lower alkyl group, a cycloalkyl group, or a substituted or unsubstituted phenyl-lower alkyl group, R^{14} is a lower alkyl group, a lower alkenyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, or a hydroxy-lower alkyl group, and Z is the same as defined above,

provided that when R^{13} is a hydrogen atom, then reacting with the compound (X), and when R^{23} is a hydrogen atom, then reacting with the compound (XI), and if necessary, followed by removing the protecting groups from the product, and if necessary, converting the product thus obtained into a pharmaceutically acceptable acid addition salt thereof.

12. A pharmaceutical composition, which contains as an active ingredient the 2-aryl-8-oxodihydropurine derivative as set forth in any one of claims 1-10, or a pharmaceutically acceptable acid addition salt thereof.

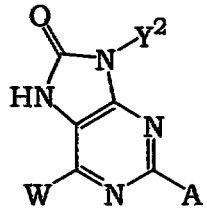
13. An agent for treatment of anxiety-related diseases, which contains as an active ingredient the 2-aryl-8-oxodihydropurine derivative as set forth in any one of claims 1-10, or a pharmaceutically acceptable acid addition salt thereof.

14. A method for treatment of anxiety-related diseases such as neurosis, somatoform disorders, and anxiety disorders, which comprises administering an effective amount of the 2-aryl-8-oxodihydropurine derivative as set forth in any one of claims 1-10, or a pharmaceutically acceptable acid addition salt thereof, to a patient with anxiety-related diseases.

15. Use of the 2-aryl-8-oxodihydropurine derivative as set forth in any one of claims 1-10, or a pharmaceutically acceptable acid addition salt thereof, in the treatment of a patient with anxiety-related diseases such as neurosis, somatoform disorders, and anxiety disorders.

16. An anxiolytic agent, which contains as an active ingredient the 2-aryl-8-oxodihydropurine derivative as set forth in any one of claims 1-10, or a pharmaceutically acceptable acid addition salt thereof.

17. A 2-aryl-8-oxodihydropurine derivative of the formula (II):



(II)

wherein W is a hydrogen atom, a lower alkyl group, a halogen atom, a lower alkoxy group, an amino group, a mono- or di-lower alkylamino group, or a substituted or unsubstituted phenyl group, Y^2 is a hydrogen atom, a lower alkyl group, a cycloalkyl group, a cycloalkyl-lower alkyl group, a lower alkenyl group, or a substituted or unsubstituted phenyl-lower alkyl group, and A is a substituted or unsubstituted phenyl group, or a substituted or unsubstituted heteroaryl group.