DESCRIPTION

5-SUBSTITUTED-3-OXADIAZOLYL-1,6-NAPHTHYRIDIN-2(1H)-ONE DERIVATIVES

TECHNICAL FIELD

The present invention relates to novel a 5-substituted-3-oxadiazolyl-1,6-naphthyridin-2(1H)-one derivative or a pharmaceutically acceptable acid addition salt thereof which is useful as a medicament, and use thereof as a medicament, and further intermediates for preparing the same.

BACKGROUND ART

Benzodiazepine (BZP) compounds, such as diazepam which is a representative compound, have anxiolytic activity and hence have been developed as anxiolytic drugs, but they have also anticonvulsant, sedative and hypnotic activities and hence these compounds have been used in wide clinical fields such as (1) anxiolytic drug, (2) sedative (hypnotic) drug, (3) muscular relaxant, and (4) antiepileptic drug.

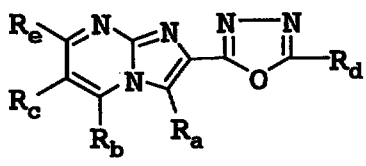
BZP compounds have mainly the pharmacological activities such as (1) acclimating activity, (2) hypnotic activity, (3) central muscle relaxant activity, (4) anti-convulsant activity. It is understood that these activities are not exhibited by independent mechanism separately, but are induced by closely related neuropharmacological mechanisms.

Since late 1970s, with progress of pharmacological investigation of BZP compounds, there have been found two footings for clarifying the mechanism of exhibiting the activities thereof, one being a phenomenon of increasing γ-aminobutyric acid agonistic (GABAergic) neurotransmittant mechanism of the central nervous system by the BZP drugs, and another being new finding of BZP specific binding site (BZP receptor) and proving of a mechanism of the functional connection between the brain BZP receptor and GABA receptor. As the result of such investigation, it has almost been established that the GABAergic neurotransmittant mechanism participates in the pharmacological activities of BZP compounds.

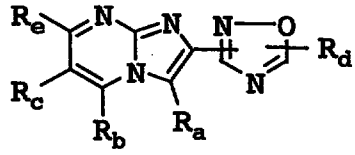
Administration of BZP compounds induces side effects such as ataxia, hypnosis, muscle relaxation or lowering of ability of cognition or reflex movement and further formation of resistance and dependence to the drugs, and hence, there are many problems to be improved in the BZP compounds. Studies have been made on non-BZP compounds which have a different chemical structure from BZP compounds but have similar functions in the activation mechanisms. Those compounds including such non-BZP compounds are called as benzodiazepine receptor agonistic drugs. As the non-BZP compounds, there are known, for example, the compounds having the chemical formulae (A), (B) and (C) as shown below.

The compounds having the formulae (A) and (B) are disclosed

in Journal of Medicinal Chemistry, vol. 34, p. 2060 (1991).



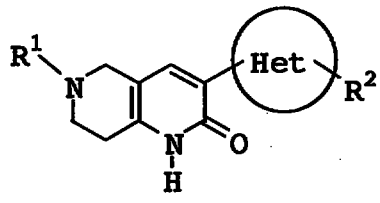
(A)



(B)

wherein R_a is a hydrogen atom, R_b - R_d are a methyl group, etc., and R_e is a methoxy group, etc.

The compounds of the formula (C) are disclosed in EP-A2-0588500.



(C)

wherein Het is an oxadiazolyl group, R^1 is a benzyl group, etc. and R^2 is a methoxy group, etc.

However, with progress of investigation, there has been found a certain compound among the non-BZP compounds, which has similar high selective affinity to the benzodiazepine (BZP) receptor but has entirely inverse activities [Braestrup, C. et al., Neuropharmacol., 22, pp.1451-1457 (1983)]. When these compounds are administered, they exhibit pharmacological activities such as convulsion increasing activity, anxiety inducing activity, muscle hypertonia. Accordingly, the old BZP compounds which have hitherto been used as anxiolytic drugs are

defined as an agonist, and the compounds having thus inverse activities are defined as an inverse agonist.

Since these inverse agonists have been found, intensive studies have been done on the correlation between the modifying (binding) manner and the pharmacological activities of the compounds which bind (exhibit affinity) to the BZP receptor. According to these studies, it has been found that the BZP receptor is present between the GABA receptor (an depressive neurotransmittant) and a chloride ion channel and is a molecular unit to form a complex. The GABA receptor includes an ion channel type $GABA_A$ receptor and a metabolism controlling type $GABA_B$ receptor, and the $GABA_A$ receptor forms a complex with a BZP receptor and the Cl ion channel. The compounds to be bound to the BZP receptor are now classified into an agonist (further subsequently classified into a full agonist and a partial agonist), an inverse agonist (further subsequently classified into a full inverse agonist and a partial inverse agonist) and an antagonist.

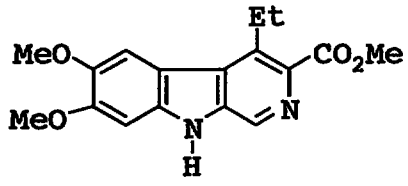
The agonist binds selectively to the BZP compounds and thereby acts increasing coupling of the GABA receptor and the Cl ion channel and increases flowing of Cl ion into cells owing to increase of open-close frequency of the Cl ion channel and then stimulates the cell activities owing to decrease of negative electric charge (increases cell stimulation). It is said that the antagonist does not change the coupling function thereof but

inhibits binding of the agonist or inverse agonist to the BZP receptor.

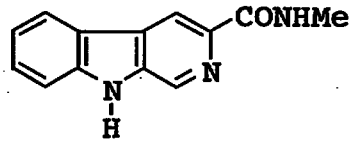
There are many method for checking the manner of binding of the compounds to the benzodiazepine receptor, and one of the known methods is a TBPS binding assay. As mentioned hereinbefore, the $GABA_A$ receptor forms a complex with a BZP compound receptor and the Cl ion channel, and it is known that a neurosteroid receptor is present on the $GABA_A$ receptor membrane and a TBPS(t-butylbicyclophosphonothionate) bond recognizing site is located around the Cl ion channel. The function of GABA to the nervous system is modified and controlled by controlling of the opening of the Cl ion channel and transmission of Cl ion into cells within the $GABA_A$ receptor complex molecule under complicated mutual effects. By checking many drugs which act directly or indirectly on the function of the $GABA_A$ receptor complex, it is known that there is a good inverse correlation between the test data of TBSP binding and the test data of Cl ion uptake into cells. For instance, the uptake of Cl ion into cells is decreased by $GABA_A$ receptor agonists (e.g. Muscimol), neurosteroid receptor agonists, diazepam which is the representative benzodiazepaine receptor agonist, or chlonazepam which is a partial agonist, and is increased by benzodiazepine receptor inverse agonist [e.g. DMCM (methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate)] and a partial inverse agonist [e.g. FG7142 (N-methyl-β-carboline-3-carboxamide)].

Accordingly, the TBPS binding assay is useful for clarifying the $GABA_A$ receptor function, the in vitro biochemical screening of the drugs acting via allosteric binding site of bezodiazepine drugs, $GABA_A$ receptor complex, etc., and the acting mechanisms of the drugs.

Most of the old BZP compounds such as the compounds of the formulae (A), (B) and (C) have agonistic properties. On the contrary, some compounds having inverse agonistic properties are known, for example, the compounds of the following formulae (D) and (E) (DMCM and FG7142):



(D)
DMCM



(E)
FG7142

The DMCM and FG7142 are disclosed in Colin R. Gardner, Drugs of the Future, vol. 14, pp. 51-67 (1987).

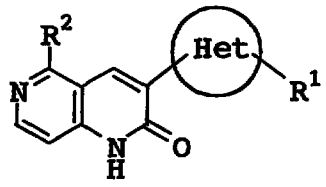
In addition, many investigations have also been made on the correlation between the binding manner to the benzodiazepine receptor and the pharmacological activities of the compounds. As mentioned above, the BZP agonists have been used as anxiolytic drug, hypnotic disorder curing agent (sleep inducing drug) or antiepileptic drug, but it is known that in addition to these activities, they have also an amnestic activity in animals including also human being. Accordingly, BZP inverse agonists are expected to have activities inverse to the amnesia inducing

activity, that is, anti-amnestic activity, psychoanaleptic activity. Moreover, it is known that the activity of acetylcholine, which has an important relation to cognition function, is decreased by the BZP agonists and is increased by the BZP inverse agonists, and hence the BZP inverse agonists are expected to exhibit cognition enhancing activity. Thus, it has been expected that the BZP inverse agonists may be useful as psychoanaleptic drug and a drug for treating dysmnesia in senile dementia, cerebrovascular and Alzheimer's dementia.

There is no report as to the compounds of the present invention which have the formula (I) described hereinafter and have high selective affinity to a benzodiazepine receptor and particularly acts as a BZP inverse agonist.

DISCLOSURE OF THE INVENTION

This invention provides a novel 5-substituted-3-oxadiazolyl-1,6-naphthyridin-2(1H)-one derivative having the following formula (I) or a pharmaceutically acceptable acid addition salt thereof which has high selective affinity to a benzodiazepine receptor, and a use thereof as a medicament.



(I)

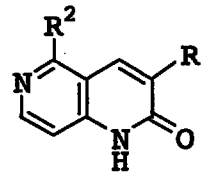
wherein Het is an oxadiazolyl group,

R^1 is a hydrogen atom, a lower alkyl group, a cyclo-lower alkyl group, a trifluoromethyl group, a lower alkenyl group, a

lower alkynyl group, a lower alkoxy group, a lower alkoxy-lower alkyl group, a hydroxy-lower alkyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaromatic group, and

R^2 is a hydrogen atom, a lower alkyl group, a cyclo-lower alkyl group, a cyclo-lower alkylmethyl group, a lower alkenyl group, a cyclo-lower alkenyl group, a lower alkynyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaromatic group.

This invention further provides novel 1,6-naphthyridin-2(1H)-one derivatives of the following formula (I') which are useful as an intermediate for preparing 5-substituted-3-oxadiazolyl-1,6-naphthyridin-2(1H)-one derivatives of the above formula (I) useful as a medicament.



(I')

wherein R is a cyano group, a carbamoyl group, a carboxyl group, a lower alkoxycarbonyl group, or a substituted or unsubstituted benzyloxycarbonyl group, and

R^2 is a lower alkyl group, a cyclo-lower alkyl group, a lower alkenyl group, a cyclo-lower alkenyl group, a lower alkynyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaromatic group, provided that R^2 is not a methyl group or a pyridyl group.

During the intensive studies of non-benzodiazepine compounds having affinity to an intracerebral benzodiazepine receptor, the present inventors have found that the 5-substituted-3-oxadiazolyl-1,6-naphthyridin-2(1H)-one derivatives of the above formula (I) have a high selective affinity to a benzodiazepine (BZP) receptor and hence are useful as a benzodiazepine receptor agonistic drug and further that those compounds include a compound having a BZP agonistic activity and a compound having a BZP inverse agonistic activity which depend on the kinds of combination of the substituents R^1 and R^2.

Among the compounds of this invention, preferred compounds are the compounds of the formula (I) wherein R^1 is a C_1-C_3 alkyl group, a C_3-C_4 cycloalkyl group, or a C_2-C_3 alkenyl group, and R^2 is a hydrogen atom, a C_1-C_4 alkyl group, a C_3-C_6 cycloalkyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaromatic group.

More preferred compounds are the compounds of the formula (I) wherein R^1 is a C_1-C_3 alkyl group or a C_3-C_4 cycloalkyl group, and R^2 is a hydrogen atom, a C_1-C_3 alkyl group, a C_3-C_4 cycloalkyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted heteroaromatic group.

Further preferred compounds are the following compounds.

3-(5-Ethyl-1,2,4-oxadiazol-3-yl)-5-(2-methylcyclopropyl)-1,6-naphthyridin-2(1H)-one,

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(2-methylphenyl)-1,6-naphthyridin-2(1H)-one,

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(3-methoxyphenyl)-1,6-naphthyridin-2(1H)-one,

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(4-methoxyphenyl)-1,6-naphthyridin-2(1H)-one,

3-(5-Ethyl-1,2,4-oxadiazol-3-yl)-5-(2-thienyl)-1,6-naphthyridin-2(1H)-one,

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(4-pyridyl)-1,6-naphthyridin-2(1H)-one,

3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-methyl-1,6-naphthyridin-2(1H)-one,

3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-(3-fluorophenyl)-1,6-naphthyridin-2(1H)-one,

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-5-(3-methylphenyl)-1,6-naphthyridin-2(1H)-one,

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-5-(3-methoxyphenyl)-1,6-naphthyridin-2(1H)-one,

3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-(4-methoxyphenyl)-1,6-naphthyridin-2(1H)-one,

3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-(4-pyridyl)-1,6-naphthyridin-2(1H)-one, and

3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-5-(3-thienyl)-1,6-naphthyridin-2(1H)-one.

The pharmaceutically acceptable acid addition salt of the

compounds of the formula (I) includes inorganic acid addition salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, and organic acid addition salts such as oxalate, maleate, fumarate, malonate, lactate, malate, citrate, tartrate, benzoate, methanesulfonate, or tosylate.

In the specification, the terms "lower alkyl group" and the "lower alkyl" moiety mean a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, and hexyl groups.

The term "cyclo-lower alkyl group" means a cycloalkyl group having 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups, where the ring may be substituted by a C_1-C_3 alkyl group or a halogen atom.

The terms "lower alkenyl group" and the "lower alkynyl group" have a straight or branched chain having 2 to 6 carbon atoms, and include, for example, allyl, 1-propenyl, propargyl, and 2-methyl-1-ethynyl groups.

The term "cyclo-lower alkenyl group" means a cycloalkyl group having 5 to 6 carbon atoms, for example, cyclohexenyl group.

The terms "lower alkoxy group" and the "lower alkoxy" moiety mean a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, and include, for example, methoxy, ethoxy, propoxy, isopropyloxy, butyloxy, isobutyloxy, tert-butyloxy, pentyloxy, and hexyloxy groups.

The terms "aryl group" and "aryl" moiety mean a phenyl group or a naphthyl group and the ring thereof may optionally have a 1 to 3 substituents selected from a halogen atom, a C_1-C_3 alkyl group, a trifluoromethyl group, a hydroxy group, a C_1-C_3 alkoxy group, a trifluoromethoxy group, a cyano group and an amino group, and a nitro group.

The term "heteroaromatic group" means a 5- or 6-membered aromatic heterocyclic group containing, the same or deifferent, 1 to 2 hetero atoms selected from nitrogen atom, oxygen atom, and sulfur atom, and includes, for example, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, pyridyl, pyridazinyl, and pyrimidinyl, which these heteroaromatic groups may optionally have 1 to 3 substituents selected from a halogen atom, a C_1-C_3 alkyl group, a hydroxy group, a C_1-C_3 alkoxy group, and an amino group.

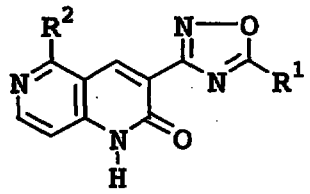
In the "substituted or unsubstituted benzyloxycarbonyl group", the substituent is selected from a C_1-C_3 alkyl group, a C_1-C_3 alkoxy group, a cyano group and a nitro group.

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

The compounds of this invention may be prepared by the processes 1 to 4 as mentioned below.

(Process 1)

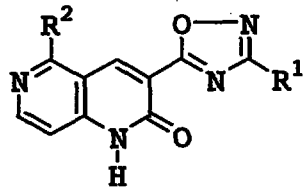
In the compound of the formula (Ia):



(Ia)

wherein R^1 and R^2 are the same as defined above,

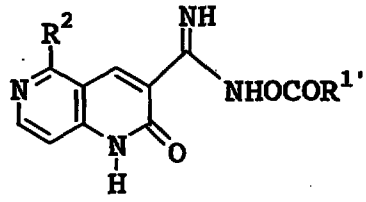
or of the formula (Ib):



(Ib)

wherein R^1 and R^2 are the same as defined above,

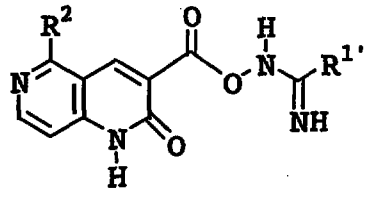
when R^1 is a group other than a lower alkoxy group, the compound can be prepared by subjecting a compound of the formula (II):



(II)

wherein $R^{1'}$ is the same as R^1 other than lower alkoxy group, and R^2 is as defined above,

or of the formula (III):



(III)

wherein $R^{1'}$ is the same as R^1 other than lower alkoxy group, and R^2 is as defined above,

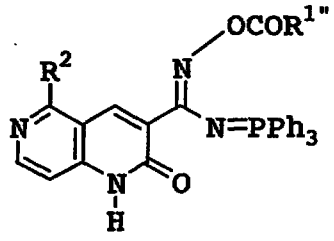
to an intramolecular cyclization reaction.

The cyclization reaction may be carried out in the presence of a dehydrating agent, but may usually be carried out by heating

the compound in an appropriate solvent which does not affect the reaction. The solvent includes aromatic hydrocarbons (e.g. benzene, toluene, xylene), ethers (e.g. tetrahydrofuran, dioxane), N,N-dimethylformamide. These solvents may be used alone or in combination of two or more thereof. The reaction temperature may vary depending on the kinds of the starting materials, etc. but is usually in the range of 50 to 150°C, preferably 80 to 120°C.

(Process 2)

In the compound of the formula (Ia), when R^1 is a lower alkoxy group, the compounds can be prepared by subjecting a compound of the formula (IV):



(IV)

wherein $R^{1''}$ is a lower alkoxy group, Ph means a phenyl group, and R^2 is the same as defined above,

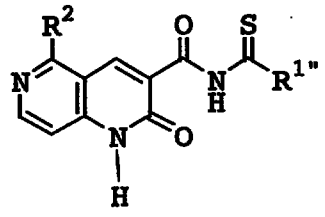
to an intramolecular cyclization reaction in a similar manner as described, for example, in Synthesis, p.843 (1986).

The cyclization reaction is usually carried out by heating the starting compound in an appropriate solvent. The solvent includes aromatic hydrocarbons (e.g. benzene, toluene, xylene), ethers (e.g. tetrahydrofuran, dioxane). The reaction temperature may vary depending on the kinds of the starting

materials, etc. but is usually in the range of 50 to 150°C, preferably 80 to 120°C.

(Process 3)

In the compound of the formula (Ib), when R^1 is a lower alkoxy group, the compound can be prepared by reacting a compound of the formula (V):



(V)

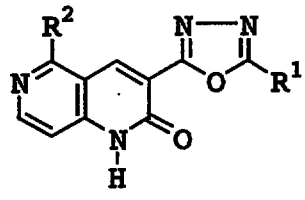
wherein $R^{1"}$ is a lower alkoxy group, and R^2 is the same as defined above,

with a hydroxylamine in a similar manner as described, for example, in Journal of Heterocyclic Chemistry, vol. 18, p.1197 (1981).

The reaction is usually carried out in an appropriate solvent. The solvent includes alcohols (e.g. methanol, ehtanol), water. The reaction temperature may vary depending on the kinds of the starting materials, etc. but is usually in the range of 50 to 90°C.

(Process 4)

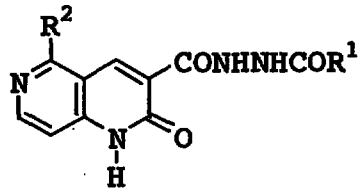
The compound of the formula (Ic):



(Ic)

wherein R^1 and R^2 are the same as defined above,

can be prepared by subjecting a compound of the formula (VI):



(VI)

wherein R^1 and R^2 are the same as defined above,

to an intramolecular cyclization reaction.

The cyclization reaction may be carried out in the presence of a dehydrating agent, but may usually be carried out by heating the compound in an appropriate solvent which does not affect the reaction. The solvent includes aromatic hydrocarbons (e.g. benzene, toluene, xylene), ethers (e.g. tetrahydrofuran, dioxane), N,N-dimethylformamide. These solvents may be used alone or in combination of two or more thereof. The reaction temperature may vary depending on the kinds of the starting materials, etc. but is usually in the range of 50 to 150°C, preferably 80 to 120°C.

The cyclization reaction may also be carried out in a similar manner as described in EP-A2-0588500 in an appropriate solvent which does not affect the reaction in the presence of a trivalent phosphorus compound (e.g. triphenylphosphine) and a dialkylazodicarboxylic acid ester. The reaction temperature may vary depending on the kinds of the starting materials, etc. but is usually in the range of 0 to 110°C, preferably 0 to 60°C.

The compounds (I) of this invention prepared by the above processes 1 to 4 may be isolated and purified by a conventional procedures such as chromatography, recrystallization, or re-

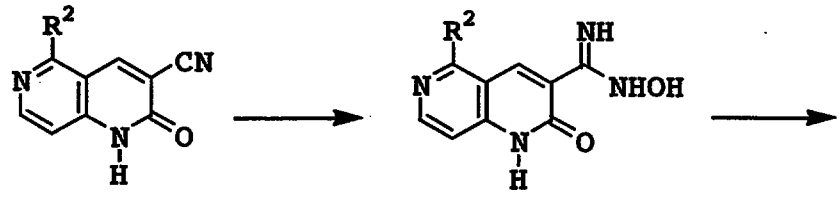
precipitation.

The compounds (I) of this invention may be obtained in the form of a free base or an acid addition salt thereof depending, for example, on the kinds of the selected starting materials to be used, on the reaction conditions and procedures. The acid addition salt may be converted into a free base by treating it by a conventional base such as an alkali metal carbonate and an alkali metal hydroxide. In addition, the free base may be converted into an acid addition salt by treating it with a kind of various acids in a usual manner.

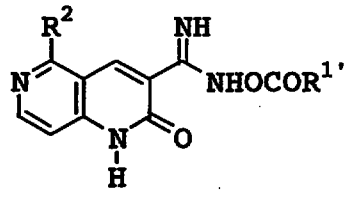
The processes for preparing the starting compounds are explained below.

The compounds of the formulae (II) to (VI) used in the above Processes 1 to 4 are novel compounds and can be prepared by a process as shown in the following Reaction Scheme-1.

Reaction Scheme-1



(1) (2)



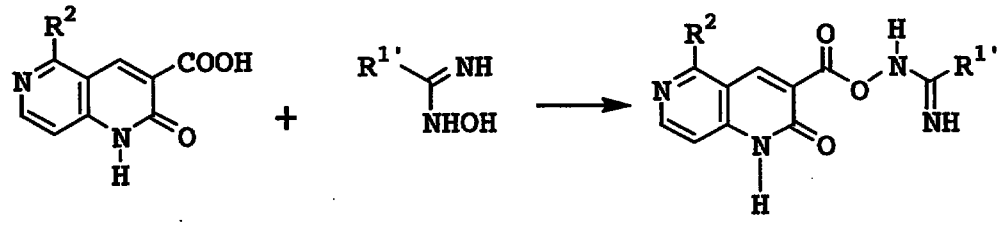
(II)

wherein $R^{1'}$ is the same as R^1 except a lower alkoxy group, and R^2 is the same as defined above.

The compound (1) is reacted with hydroxylamine in a usual manner to give the compound (2), and said compound is reacted with a reactive derivative at the carboxyl group of a carboxylic acid of the formula: $R^{1'}COOH$ (wherein $R^{1'}$ is as defined above) in the presence of a base to give the compound of the formula (II).

The compound of the formula (III) used in the above Process 1 may be prepared by a process as shown in the following Reaction Scheme-2.

Reaction Scheme-2



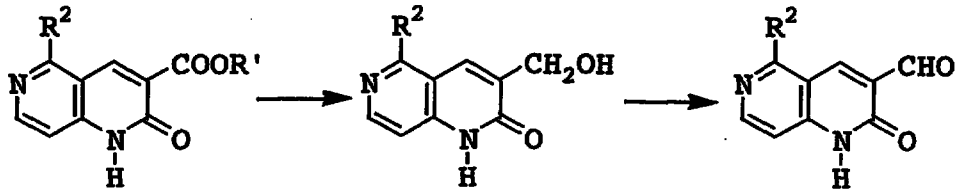
(3) (4) (III)

wherein $R^{1'}$ is the same as R^1 except a lower alkoxy group, and R^2 is the same as defined above.

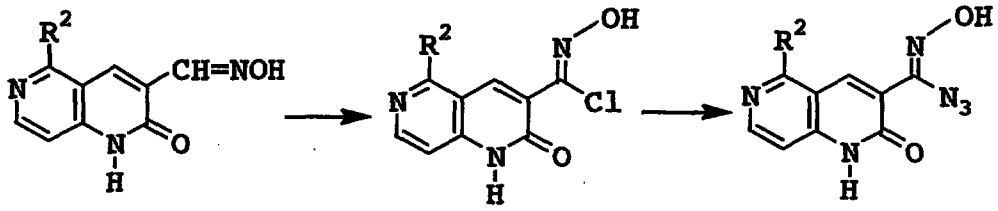
The compound (3) or a reactive derivative at the carboxyl group thereof is reacted with a kind of various amidoximes (4) under a reaction condition for a conventional amidation to give the compound of the formula (III).

The compound of the formula (IV) used in the above Process 2 can be prepared by a process as shown in the following Reaction Scheme-3.

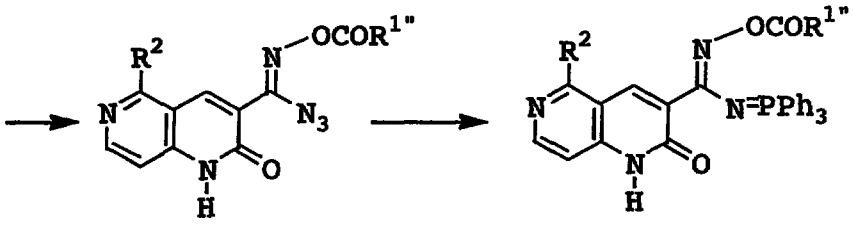
Reaction Scheme-3



(5) (6) (7)



(8) (9) (10)



(11) (IV)

wherein $R^{1"}$ is a lower alkoxy group, R' is a lower alkyl group or a substituted or unsubstituted benzyl group, Ph means a phenyl group and R^2 is the same as defined above.

The compound (5) is reduced with a reducing agent such as sodium borohydride, tetrabutylammonium borohydride, lithium aluminum hydride in an appropriate solvent to give the compound (6) and then said compound is oxidized with an activated manganese dioxide in an appropriate solvent to give the compound (7).

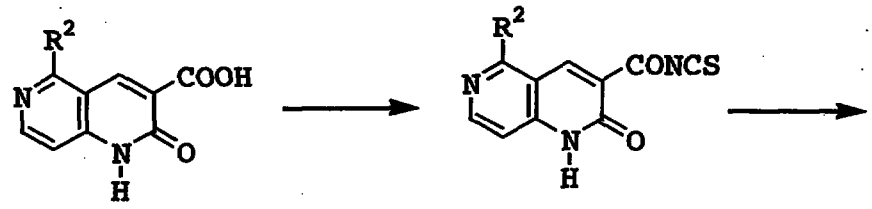
The compound (7) is reacted with hydroxylamine under a condition for the conventional oxime-forming reaction to give

the compound (8), and then said compound is reacted with N-chlorosuccinimide in a similar manner as described, for example, in Journal of Organic Chemistry, vol. 45, p.3916 (1980) to give the compound (9).

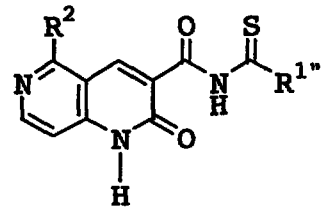
The compound (9) is reacted with sodium azide in an appropriate solvent in a similar manner as described, for example, in Synthesis, p.102 (1979) to give the compound (10), and then, said compound is reacted with a compound of the formula: $XCOR^{1"}$ (wherein X is a halogen atom and $R^{1"}$ is a lower alkoxy group) in an appropriate solvent in a similar manner as described, for example, in Synthesis, p.843 (1986) to give the compound (11), and said compound is further reacted with triphenylphosphine to give the compound of the formula (IV).

The compound of the formula (V) used in the above Process 3 can be prepared by a process as shown in the following Reaction Scheme-4.

Reaction Scheme-4



(3) (12)



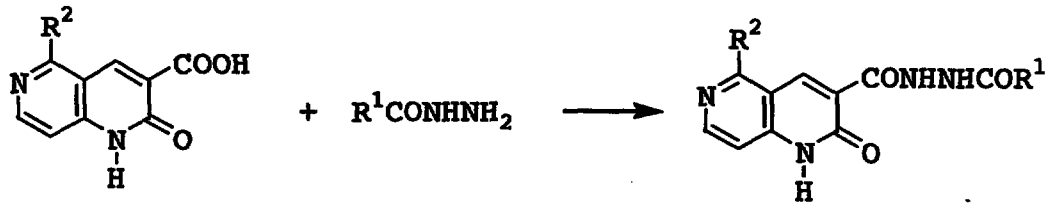
(V)

wherein $R^{1"}$ is a lower alkoxy group and R^2 is the same as defined above.

The compound (3) or a reactive derivative at the carboxyl group thereof is reacted with an alkali metal thiocyanate in an appropriate solvent to give the compound (12) and then said compound is subjected to alcoholysis to give the compound (V).

The compound of the formula (VI) used in the above Process 4 can be prepared by a process as shown in the following Reaction Scheme-5.

Reaction Scheme-5



(3) (13) (VI)

wherein R^1 and R^2 are the same as defined above.

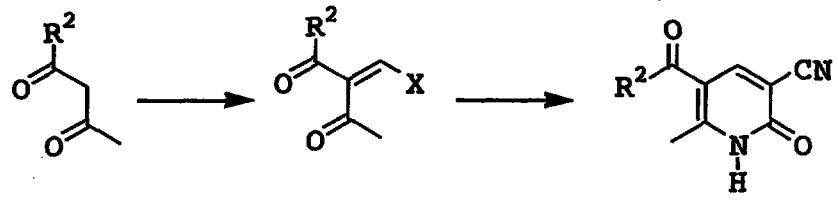
The compound (3) or a reactive derivative at the carboxyl group thereof is reacted with a hydrazide (13) of the formula: $R^1CONHNH_2$ (wherein R^1 is the same as defined above) by a conventional amidation reaction to give the compound of the formula (IV).

The compound (VI) may also be prepared by a two step reaction, that is, by reacting the compound (3) or a reactive derivative at the carboxyl group thereof with the hydrazine by a conventional amidation reaction, followed by reacting the resultant with a reactive derivative at the carboxyl group of a carboxylic acid of the formula: R^1COOH (R^1 is the same as defined above).

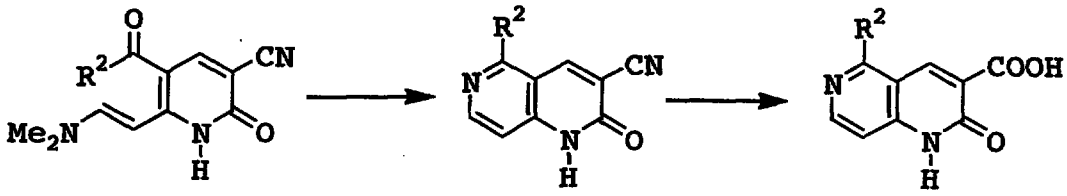
A process for preparing the intermediate of the formula (I') is explained below.

The compounds of the formula (I') wherein R is a cyano group or a carboxyl group, that is, the compound (1) and the compound (3) as used in the Reaction Scheme-1 and Reaction Scheme-2, can be prepared in a similar manner as described, for example, in Journal of Heterocyclic Chemistry, vol. 27, p.2085 (1990) or Journal of Medicinal Chemistry, vol. 35, p.4858 (1992) as shown in the following Reaction Scheme-6.

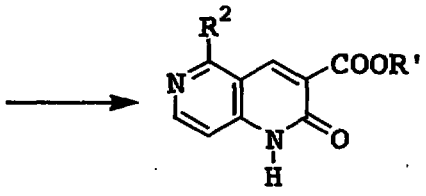
Reaction Scheme-6



(14) (15) (16)



(17) (1) (3)



(5)

wherein X is a di-lower alkylamino group, a cyclic amino group, a hydroxy group, a halogen atom, or a lower alkoxy group, R' is a lower alkyl group or a substituted or unsubstituted benzyl group, and R^2 is the same as defined above.

In the above reaction scheme, the compound (16) can be prepared by reacting the compound (14) with N,N-dimethylformamide dimethylacetal or an orthoformic acid ester in an appropriate solvent in a similar manner as described, for example, in Heterocycles, vol. 29, p.1517 (1989) or in Journal of Heterocyclic Chemistry, vol. 27, p.511 (1990) to give the compound (15), followed by reacting it with cyanoacetamide in the presence of an appropriate base.

The compound (16) thus prepared is further reacted with N,N-dimethylformamide dimethylacetal in an appropriate solvent to give the compound (17), and then said compound is reacted with ammonia or an ammonium salt in an appropppriate solvent to give the compound (1). The compound (1) thus obtained is hydrolyzed with an acid or an alkali by a conventional method to give the compound (3).

In addition, the compounds of the formula (I') wherein R is a lower alkoxycarbonyl group or a substituted or unsubstituted benzyloxycarbonyl group, for example, the compounds (5) can be prepared by esterifying the compound (1) or the compound (3) by a conventional method.

Pharmacological Experiments

The pharmacological properties of the compounds (I) of the present invention are illustrated by the following experiments with representative compounds.

Experiment 1 Benzodiazepine Receptor Binding Assay

According to the method disclosed in Life Science Vol. 20, p. 2101 (1977), the benzodiazepine receptor binding assay was carried out.

A crude synaptosome membrane fraction prepared from brains of Wistar rats (age: 7 to 8 weeks) was suspended in 15 mM Tris-HCl buffer (pH 7.4) containing 118 mM sodium chloride, 4.8 mM potassium chloride, 1.28 mM calcium chloride and 1.2 mM magnesium sulfate in a concentration of 1 g (wet weight) of brain per 20

ml of buffer to give a receptor membrane source. [3H]-diazepam was used as a labelled ligand.

A test compound (a known amount), [3H]-diazepam (final concentration; 1.5 nM), receptor membrane and the above buffer were added to a test tube (final volume: 1 ml). The reaction was started by addition of the receptor membrane. The test tube was incubated at 0°C for 20 minutes, and the reaction mixture was terminated by rapid filtration through Whatman GF/B glass fiber filter attached to a Cell-harvester (manufactured by Brandell). Immediately, the collected labelled ligand-bound receptor membrane was washed three times with ice-cold 50 mM Tris-HCl buffer (pH 7.7, each 5 ml). The radioactivity on the filter was measured by a liquid scintillation counter to determine the amount of the [^{3}H]-diazepam bound to the receptor membrane (total binding). Separately, the same procedures were repeated except 1 μM diazepam was added, and thereby the amount of [^{3}H]-diazepam bound to the receptor membrane (non-specific binding) was measured likewise. This non-specific binding was deducted from the total binding to give the specific binding. Based on the specific binding thus obtained, the inhibitory activity (IC50) of the test compound was determined by probit method.

The results are shown in the following Tables 1 to 4.

Table 1

BENZODIAZEPINE RECEPTOR BINDING Assay

Ex. No.	BZP-receptor Binding IC_{50}(nM)	Ex. No.	BZP-receptor Binding IC_{50}(nM)
1	2.28	26	0.67
3	3.58	27	0.96
4	1.65	28	1.25
5	1.64	29	5.28
6	2.98	31	1.64
7	2.39	32	3.29
9	1.62	33	5.50
10	8.08	37	3.91
11	9.77	38	1.31
12	7.89	39	2.86
14	9.45	40	7.45
15	6.16	44	2.62
16	3.69	45	0.96
17	0.69	46	2.15
18	2.04	47	2.33
19	6.37	48	1.49
20	2.77	49	1.11
21	4.21	50	0.88
22	3.76	51	0.79
23	1.76	52	0.74
24	4.47	54	1.21
25	1.84	55	1.66

Table 2

Ex. No.	BZP-receptor Binding IC_{50}(nM)	Ex. No.	BZP-receptor Binding IC_{50}(nM)
56	2.71	104	5.18
57	1.55	105	1.08
58	1.52	106	1.96
59	1.98	107	6.56
60	2.01	108	2.14
61	1.04	109	1.75
86	2.21	110	1.16
87	2.35	111	2.06
88	4.63	112	2.68
89	10.5	113	2.18
91	0.61	114	1.08
92	0.75	115	1.52
93	1.75	116	1.17
94	4.49	117	1.41
95	1.09	118	1.28
96	2.82	119	2.53
97	4.64	120	1.59
98	8.56	121	0.78
99	1.67	122	0.87
100	1.31	123	1.12
102	0.81	173	0.94
103	0.83	175	1.21

Table 3

Ex. No.	BZP-receptor Binding IC_{50}(nM)	Ex. No.	BZP-receptor Binding IC_{50}(nM)
176	2.13	203	1.97
176	2.33	204	5.51
178	2.31	205	4.77
179	4.73	206	1.16
180	1.22	207	3.42
183	1.55	208	4.14
186	1.55	209	1.28
187	6.42	210	3.41
188	1.20	211	0.82
189	0.84	212	1.26
190	1.57	213	2.07
192	4.22	215	2.47
193	4.10	216	1.17
194	1.06	217	1.34
195	4.01	218	2.58
196	4.60	219	2.03
197	1.97	220	0.93
198	1.03	221	0.72
199	1.55	222	1.49
200	0.92	224	3.57
201	1.84	225	2.12
202	2.09	226	1.41

Table 4

Ex. No.	BZP-receptor Binding IC_{50}(nM)
227	1.46
228	1.59
229	1.12
230	0.9
231	0.71
232	6.48
233	1.58
234	0.84
235	0.91
236	1.61
237	1.86
238	1.38
240	2.51
241	6.08
242	1.87
243	1.81
244	4.12
245	0.81
246	1.46
247	1.39
311	1.91

Experiment-2 TBPS Binding Assay

(Method)

The TBPS (t-butylbicyclophosphonothionate) binding assay and the preparation of the membrane specimen were done in a similar manner to the method of Biggio, G. et al. [cf. European Journal of Pharmacology, vol. 161, pp.173-180 (1989)].

The membrane specimen was prepared from the cerebral cortex of Wistar rats (age: 7 to 8 weeks) by the following procedure. That is, to the cerebral cortex was added a 50-fold volume of an ice-cooled buffer (a 50 mM Tris-citrate buffer containing 100 mM sodium chloride, pH 7.4) and the mixture was homogenized at 0 - 4°C and then centrifuged at 20,000g for 20 minutes. The pellets thus obtained were once subjected to homogenization in a buffer and centrifugation by the same procedure as above and then kept in freezed state at -80°C for more than 20 hours. On the test day, the freezed pellets were thawed and then subjected twice to the homogenization-centrifugation procedure as described above. The pellets thus obtained were suspended in a buffer in a concentration of 1 g (wet weight) per 25 ml of buffer to give a membrane specimen to be used in the binding assay.

The binding assay was carried out by the following procedure by using as a labelled ligand [^{35}S]TBPS (final concentration; 0.4 nM) and as a non-labelled ligand Picrotoxin (final concentration; 100 μM) in the presence of GABA (final

concentration; 1 μM).

A test compound (a known amount), [^{35}S] labelled ligand, the membrane specimen, GABA and a buffer were added to a test tube (final volume; 1 ml). The reaction was started by addition of the membrane specimen (200 μl). The test tube was incubated at 25°C for 90 minutes, and the reaction was terminated by filtration through Wattman GF/B glass fiber filter (which was previously dipped in 0.01% polyethylenimine for one day) attached to a Cell-harvester (manufactured by Brandell), and thereby, the labelled ligand-bound membrane was collected onto the filter. Immediately, the collected labelled ligand-bound membrane was washed with a ice-cooled 50 mM Tris-HCl buffer (pH 7.7, each 5 ml) three times. Subsequently, the filter was moved into a liquid scintillation vial and thereto was added a liquid scintillation cocktail (ACS-II, manufactured by Amersham, USA, 10 ml) and allowed to stand for a fixed period of time. Thereafter, the radioactivity on the filter was measured by a liquid scintillation counter (2000CA type, manufactured by Paccard, USA) to determine the total binding amount. Separately, the same procedures were repeated in the presence of Picrotoxin to determine the non-specific binding amount. The non-specific binding amount was deducted from the total binding amount to give the specific binding amount. The binding activity of the test compound was calculated by a variation rate, i.e., a rate of the specific binding amount of the test compound to the specific

binding amount in control (using a solvent).

(Evaluation criteria)

+% value means to exhibit inverse agonistic properties, -% value means to exhibit agonistic properties and 0% means to exhibit antagonistic properties.

The results are shown in Table 5 and Table 6.

Table 5

TBPS Binding Test

Ex. No.	Variation Rate (%)	Ex. No.	Variation Rate (%)
2	53	48	18
3	12	50	40
4	20	52	-11
5	21	55	-16
6	15	58	-15
7	12	86	12
8	13	87	32
11	21	88	41
13	24	89	22
14	38	91	38
16	38	92	32
17	25	93	34
18	10	94	34
20	-13	95	13
21	21	96	16
23	-23	100	-23
24	22	102	33
36	15	103	21
38	25	105	25
43	28	106	20
45	-9	107	17
47	-11	123	12

Table 6

Ex. No.	Variation Rate (%)	Ex. No.	Variation Rate (%)
173	18	194	32
175	28	196	-9
176	39	198	11
177	29	200	17
178	25	202	22
179	37	203	17
180	13	206	-13
181	13	210	15
182	19	211	24
183	8	212	27
184	17	213	26
185	19	224	-12
186	21	228	-10
187	27	229	10
188	34	233	31
189	29	240	-13
190	34	241	-14
191	18	244	-15
192	13	245	13
193	44	247	16

Experiment 3 Test of increasing activity on pentylentetrazol-induced convulsion

It is known that benzodiazepine receptor inverse agonists increase convulsion induced by pentylentetrazol [cf. Progress in Neuro-Psychopharmacology and Biological Psychiatry, vol. 12, p.951 (1988)]. Some compounds of the present invention were tested as to the activities of increasing the pentylentetrazol-induced convulsion.

A test compound (compounds disclosed in working examples) was orally administered to ddY male mice (weight; 22-25 g, five mice/group) in an amount of 5 - 100 mg/kg. Fifteen minutes later, pentylentetrazol (70 mg/kg, which amount does not induce tonic convulsion by said compound alone) was injected subcutaneously into the mice, and immediately, the mice were observed as to the appearance of tonic convulsion at the hind leg for 30 minutes. The effects were evaluated by the number of mice among five mice, of which the convulsion increasing effects were observed. The results are shown in Table 7.

Table 7

Ex. No.	Dose (mg/kg, po)	Effects (number of animals)
4	10	4/5
5	5	5/5
6	100	4/5
11	10	4/5
18	20	3/5
86	10	2/5
88	10	5/5
89	50	5/5
94	50	4/5
102	10	5/5
103	10	2/5
105	50	4/5
173	20	5/5
183	20	4/5
184	50	5/5
186	50	4/5
191	10	5/5
192	100	5/5
200	50	4/5
210	10	4/5
213	10	5/5
220	20	4/5
247	50	4/5

As is shown in the above results, compounds embodying the present invention showed high selective affinity for benzodiazepine receptor and hence are useful as a drug for acting onto benzodiazepine receptor. Although some of the compounds of this invention have also agonistic properties, the compounds of this invention are particularly useful as an inverse agonist. The compounds having inverse agonistic properties are expected to be used in clinical fields entirely different from those of agonists, for example, as a psychoanaleptic drug or a drug for the treatment of dysmnesia in senile dementia or Alzheimer's disease.

PHARMACEUTICAL USE OF THE COMPOUNDS OF THIS INVENTION

The compounds of this invention may be administered either orally, parentally or intrarectally when used as a drug for acting onto benzodiazepine receptor, but preferably orally. The dosage of the compounds varies according to the route of the administration, conditions and ages of the patients, or the types of the treatment (e.g. prophylaxis or treatment) and the like, but it is usually in the range of 0.01 to 10 mg/kg/day, preferably in the range of 0.02 to 5 mg/kg/day.

The present compounds may be administered in the form of a conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier or diluent. The pharmaceutically acceptable carrier or diluent may be any conventional one which is used in this field and does not react

with the present compound, for example, lactose, glucose, mannitol, dextran, starch, white sugar, magnesium aluminate metasilicate, synthetic aluminum silicate, crystalline cellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, hydroxypropyl starch, ion-exchange resin, methyl cellulose, gelatin, gum arabic, hydroxypropyl cellulose, lower-substituted hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, light silicic anhydride, 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, liquid paraffin, white petrolatum, nonionic surfactant, propylene glycol, water, and the like.

Pharmaceutical preparations are tablets, capsules, granules, powders, syrups, suspensions, suppositories, gels, injection preparations, and the like. These preparations may be prepared by a conventional method. When a liquid preparation is prepared, it may previously be in the form of a solid preparation which is dissolved or suspended in water or a solvent when used. In addition, tablets or granules may be coated by a conventional method, and injection preparations prepared by dissolving the compound (I) of the present invention or an acid addition salt thereof in distilled water for injection, or a physiological saline solution, but if necessary, it may be

dissolved in a isotonic solution, and further, a pH adjustor, a buffer or a preservative may be added thereto.

These pharmaceutical preparations may contain the present compound in an amount of more than 0.01 % by weight, preferably 0.05 to 70 % by weight, and may contain other pharmacologically active ingredients.

BEST MODE FOR CARRYING OUT THE INVENTION

The compounds of this invention are illustrated by the following Examples. The symbols in tables means as follows. Me: methyl, Et: ethyl, n-Pr: n-propyl, i-Pr: isopropyl, c-Pr: cyclopropyl, n-Bu: n-butyl, t-Bu: tert-butyl, Ph: phenyl. The position of substituents is indicated like this, for example, 3-Me-Ph means 3-methylphenyl.

Example 1

Preparation of 3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5-methyl-1,6-naphthyridin-2(1H)-one:

(1) To a solution of hydroxylamine hydrochloride (4.17 g) in water (50 ml) was added sodium carbonate (3.18 g) with stirring under ice cooling. To the solution were subsequently added ethanol (200 ml) and 1,2-dihydro-5-methyl-2-oxo-1,6-naphthyridine-3-carbonitrile (3.70 g), and the mixture was refluxed for 2 hours. After distilling off the solvent under reduced pressure, water was added to the residue, and the precipitated crystals were separated by filtration. The product was washed with water, isopropanol, diisopropyl ether in this

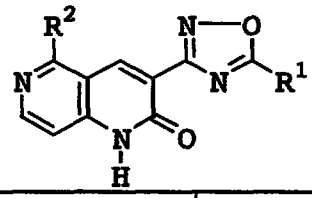
order, and dried to give 1,2-dihydro-5-methyl-2-oxo-1,6-naphthyridin-3-amidoxime (4.2 g). This compound was used in the next reaction without being purified.

(2) To a suspension of the above amidoxime (1.09 g), sodium carbonate (0.83 g) and methyl ethyl ketone (200 ml) was added cyclopropanecarbonyl chloride (0.57 g) with stirring under ice cooling, and the mixture was stirred at room temperature overnight. After distilling off the solvent under reduced pressure, water was added to the residue, and the precipitated crystals were separated by filtration, washed with water, isopropanol and diisopropyl ether in this order, and then dried. To the resulting crystals was added dimethylformamide (DMF) (50 ml) and the mixture was stirred at 130°C for 5 hours. After distilling off the solvent under reduced pressure, isopropanol was added to the residue, and the crystals were separated by filtration. The resulting crystals were recrystallized from ethanol-chloroform to give the title compound (0.65 g) as colorless crystals. M.p. 259-260°C.

Examples 2 to 85

In the same manner as described in Example 1, the corresponding starting materials were reacted to give the compounds of Examples 2 to 85 as shown in Tables 8 to 12.

Table 8



Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
2	Me	Me	>300	$CHCl_3$-EtOH
3	Me	i-Bu	231-233	MeCN
4	Me	Ph	302-303	EtOH
5	Me	3-F-Ph	>300	EtOH
6	Me	4-F-Ph	>300	EtOH
7	Me	3-Cl-Ph	>300	$CHCl_3$-MeOH
8	Me	4-Cl-Ph	>300	$CHCl_3$-MeOH
9	Me	3-Me-Ph	285-287	EtOH
10	Me	4-Me-Ph	>300	MeCN
11	Me	4-MeO-Ph	298-300	$CHCl_3$-MeCN
12	Et	H	249-251	MeCN
13	Et	Me	246-247	$CHCl_3$-EtOH
14	Et	Et	239-240	EtOH
15	Et	n-Pr	222-223	MeCN
16	Et	i-Pr	288-289	MeCN
17	Et	c-Pr	266-268	MeCN
18	Et	2-Me-c-Pr	285-287	EtOH
19	Et	n-Bu	223-225	MeCN
20	Et	i-Bu	227-229	MeCN

Table 9

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
21	Et	c-Bu	271-272	EtOH
22	Et	n-pentyl	216-218	MeCN
23	Et	c-hexyl	295-296	$CHCl_3$-MeCN
24	Et	c-hexyl-CH_2	235-237	EtOH
25	Et	3-c-hexenyl	281-282	EtOH
26	Et	Ph	289-290	EtOH
27	Et	3-F-Ph	>300	EtOH
28	Et	4-F-Ph	>300	EtOH
29	Et	3-Cl-Ph	>300	$CHCl_3$-MeOH
30	Et	4-Cl-Ph	>300	EtOH
31	Et	3-Me-Ph	290-291	$CHCl_3$-EtOH
32	Et	4-Me-Ph	>300	EtOH
33	Et	4-MeO-Ph	>300	$CHCl_3$-EtOH
34	n-Pr	Me	252-254	EtOH
35	n-Pr	Et	216-218	MeCN
36	n-Pr	i-Pr	273-274	MeCN
37	n-Pr	c-Pr	234-236	MeCN
38	n-Pr	Ph	284-285	EtOH
39	n-Pr	3-F-Ph	>300	EtOH
40	n-Pr	4-F-Ph	>300	EtOH
41	i-Pr	Me	266-267	EtOH

Table 10

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
42	i-Pr	Et	247-249	MeCN
43	i-Pr	i-Pr	265-267	MeCN
44	i-Pr	c-Pr	276-278	EtOH
45	i-Pr	Ph	280-281	EtOH
46	i-Pr	3-F-Ph	>300	EtOH
47	i-Pr	4-F-Ph	>300	EtOH
48	c-Pr	Et	233-236	MeCN
49	c-Pr	n-Pr	217-219	MeCN
50	c-Pr	i-Pr	268-269	MeCN
51	c-Pr	c-Pr	242-245	MeCN
52	c-Pr	Ph	281-282	EtOH
53	c-Pr	3-F-Ph	>300	EtOH
54	c-Pr	4-F-Ph	>300	EtOH
55	c-Pr	3-Cl-Ph	>300	EtOH
56	c-Pr	4-Cl-Ph	>300	EtOH
57	c-Pr	3-Me-Ph	274-276	EtOH
58	c-Pr	4-Me-Ph	>300	EtOH
59	c-Pr	4-MeO-Ph	297-299	EtOH
60	i-propenyl	c-Pr	265-268	MeCN
61	vinyl	c-Pr	250-252	MeCN

Table 11

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
62	i-Pr	2-Cl-Ph		
63	i-Pr	3-Cl-Ph	283-285	EtOH
64	i-Pr	4-Cl-Ph	>300	EtOH
65	i-Pr	2-Br-Ph		
66	i-Pr	3-Br-Ph	>300	$CHCl_3$-EtOH
67	i-Pr	4-Br-Ph	>300	$CHCl_3$-EtOH
68	i-Pr	2-Me-Ph	>300	MeCN
69	i-Pr	3-Me-Ph	281-283	MeCN
70	i-Pr	4-Me-Ph	293-294	EtOH
71	i-Pr	3-MeO-Ph	202-204	MeCN
72	i-Pr	3-CF_3-Ph	258-261	EtOH
73	i-Pr	n-Pr	217-219	MeCN
74	n-Bu	Ph	264-266	MeCN
75	i-Bu	Ph	281-283	MeCN
76	t-Bu	Ph	294-296	MeCN
77	c-hexyl	Ph	276-277	MeCN
78	CH_2OCH_3	Ph		
79	Ph	Ph	>300	DMF
80	2-Cl-Ph	Ph	>300	$CHCl_3$-EtOH
81	3-Cl-Ph	Ph	>300	DMF
82	4-Cl-Ph	Ph	>300	DMF

Table 12

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
83	4-Me-Ph	Ph	>300	DMF
84	3-pyridyl	Ph	>300	$CHCl_3$-EtOH
85	2-furyl	Ph	>300	EtOH

Example 86

Preparation of 3-(5-methyl-1,2,4-oxadiazol-3-yl)-5-(3-methoxyphenyl)-1,6-naphthyridin-2(1H)-one:

To a solution of acetic acid (0.90 g) in DMF (100 ml) was added N,N'-carbonyldiimidazole (2.43 g) and the mixture was stirred at 70°C for 3 hours. To the solution was added 1,2-dihydro-5-(3-methoxyphenyl)-2-oxo-1,6-naphthyridin-3-amidoxime (3.10 g) prepared in the same manner as described in Example 1(1), and the mixture was stirred at 70°C for 2 hours and further at 130°C for 1 hour. The reaction mixture was concentrated to dryness under reduced pressure, and water was added to the residue, and the precipitated crystals were separated by filtration and washed with water, isopropanol and diisopropyl ether in this order and then dried. The resulting crystals were subjected to silica gel column chromatography and eluted with chloroform-methanol (50 : 1). The resulting crystals were recrystallized from chloroform-ethanol to give the title compound (2.22 g) as colorless crystals. M.p. 286-288°C.

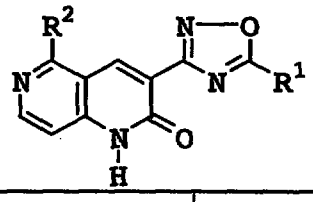
Hydrochloride of the title compound, M.p. 281-282°C

(recrystallized from ethanol).

Examples 87 to 172

In the same manner as described in Example 86, the corresponding starting materials were reacted to give the compounds of Examples 87 to 172 as shown in Tables 13 to 17.

Table 13



Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
87	Me	2-F-Ph	287-288	EtOH-i-Pr_2O
88	Me	2-Cl-Ph	262-264	$CHCl_3$-MeOH
89	Me	2-Me-Ph	244-245	MeCN
90	Me	2-MeO-Ph	260-262	MeCN
91	Me	2-furyl	291-294	MeOH
92	Me	2-thienyl	>300	$CHCl_3$-MeOH
93	Me	3-thienyl	292-294	MeCN
94	Me	4-pyridyl	>300	EtOH-i-Pr_2O
95	Et	2-F-Ph	235-236	EtOH-i-Pr_2O
96	Et	2-Cl-Ph	167-168	EtOH
97	Et	2-Me-Ph	221-222	EtOH
98	Et	2-MeO-Ph	229-230	EtOH-I-Pr_2O
99	Et	3-MeO-Ph	246-247	EtOH
100	Et	1-naphthyl	248-250	MeCN

Table 14

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
101	Et	2-naphthyl	231-233	MeCN
102	Et	2-furyl	278-280	$CHCl_3$-MeCN
103	Et	2-thienyl	291-294	$CHCl_3$-MeCN
104	Et	5-Cl-2-thienyl	280-281	$CHCl_3$-EtOH
105	Et	3-thienyl	>300	EtOH
106	Et	3-pyridyl	292-293	EtOH
107	Et	4-pyridyl	>300	$CHCl_3$-MeOH
108	n-Pr	2-F-Ph	242-243	MeCN
109	n-Pr	2-furyl	264-266	EtOH
110	n-Pr	2-thienyl	269-271	EtOH
111	n-Pr	3-thienyl	296-297	EtOH
112	i-Pr	2-F-Ph	265-267	MeCN
113	i-Pr	2-furyl	274-276	EtOH
114	i-Pr	2-thienyl	273-275	MeCN
115	i-Pr	3-thienyl	297-299	EtOH
116	c-Pr	2-F-Ph	133-135	MeCN
117	c-Pr	2-Cl-Ph	270-272	MeCN
118	c-Pr	2-Me-Ph	265-267	MeCN
119	c-Pr	2-MeO-Ph	175-177	MeCN
120	c-Pr	3-MeO-Ph	146-148	EtOH
121	c-Pr	2-furyl	280-282	$CHCl_3$-EtOH
122	c-Pr	2-thienyl	>300	$CHCl_3$-EtOH
123	c-Pr	3-thienyl	289-290	EtOH

Table 15

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
124	n-Pr	2-Cl-Ph	213-215	MeCN
125	n-Pr	3-Cl-Ph	298-300	EtOH
126	n-Pr	4-Cl-Ph	>300	EtOH
127	Me	2-Br-Ph	270-273	MeCN
128	Et	2-Br-Ph	149-151	MeCN
129	c-Pr	2-Br-Ph	260-262	MeCN
130	n-Pr	2-Br-Ph	293-296	MeCN
131	Me	3-Br-Ph	>300	$CHCl_3$-EtOH
132	Et	3-Br-Ph	>300	EtOH
133	c-Pr	3-Br-Ph	>300	$CHCl_3$-EtOH
134	n-Pr	3-Br-Ph	>300	$CHCl_3$-EtOH
135	Me	4-Br-Ph	>300	$CHCl_3$-EtOH
136	Et	4-Br-Ph	>300	EtOH
137	c-Pr	4-Br-Ph	>300	$CHCl_3$-EtOH
138	n-Pr	4-Br-Ph	>300	$CHCl_3$-EtOH
139	n-Pr	2-Me-Ph	208-210	MeCN
140	n-Pr	3-Me-Ph	226-228	MeCN
141	n-Pr	4-Me-Ph	253-255	MeCN
142	Me	2-OH-Ph		
143	Et	2-OH-Ph		
144	Me	3-OH-Ph		
145	Et	3-OH-Ph		
146	Me	4-OH-Ph		

Table 16

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
147	Et	4-OH-Ph		
148	n-Pr	2-MeO-Ph	193-194	MeCN
149	n-Pr	3-MeO-Ph	239-241	MeCN
150	Me	3-CF_3-Ph	>300	$CHCl_3$-EtOH
151	Et	3-CF_3-Ph	>300	EtOH
152	c-Pr	3-CF_3-Ph	>300	EtOH
153	n-Pr	3-CF_3-Ph	286-288	EtOH
154	Me	4-CF_3-Ph	>300	$CHCl_3$-EtOH
155	Et	4-CF_3-Ph	>300	EtOH
156	c-Pr	4-CF_3-Ph	>300	$CHCl_3$-EtOH
157	Me	3-CF_3O-Ph	>300	EtOH
158	Et	3-CF_3O-Ph	271-273	MeCN
159	c-Pr	3-CF_3O-Ph	237-239	MeCN
160	Me	4-CF_3O-Ph		
161	Et	4-CF_3O-Ph	>300	EtOH
162	c-Pr	4-CF_3O-Ph	>300	EtOH
163	Me	n-Pr	269-271	MeCN
164	Me	i-Pr	292-294	MeCN
165	Me	c-Pr	>300	MeCN
166	Me	n-Bu	232-233	MeCN

Table 17

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
167	n-Pr	n-Bu	220-222	MeCN
168	Me	c-hexyl	283-286	MeCN
169	CF_3	Ph		
170	CH_2OH	Ph		
171	2-thienyl	Ph	>300	$CHCl_3$-EtOH
172	3-furyl	Ph	>300	EtOH

Example 173

Preparation of 3-(3-ethyl-1,2,4-oxadiazol-5-yl)-5-(2-thienyl)-1,6-naphthyridin-2(1H)-one:

To a solution of 1,2-dihydro-5-(2-thienyl)-2-oxo-1,6-naphthyridin-3-carboxylic acid (3.81 g) in DMF (50 ml) was added N,N'-carbonyldiimidazole (3.41 g) and the mixture was stirred at 70°C for 4 hours. To the solution was added propionic amidoxime (1.85 g), and the mixture was stirred at 70°C for 1 hour and further at 130°C for 2 hours. The reaction mixture was concentrated to dryness under reduced pressure, and water was added to the residue, and the precipitated crystals were separated by filtration and washed with water, isopropanol and diisopropyl ether in this order and then dried. The resulting crystals were subjected to silica gel column chromatography and eluted with chloroform-methanol (50 : 1). The resulting crystals were recrystallized from chloroform-ethanol to give the

title compound (2.60 g) as colorless crystals. M.p. 265-268°C.

Examples 174 to 307

In the same manner as described in Example 173, the corresponding starting materials were reacted to give the compounds of Examples 174 to 307 as shown in Tables 18 to 24.

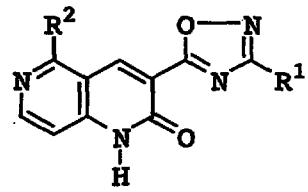


Table 18

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
174	Me	Me	>300	EtOH
175	Me	Ph	>300	EtOH
176	Me	2-F-Ph	>300	EtOH
177	Me	3-F-Ph	>300	EtOH
178	Me	4-F-Ph	>300	EtOH
179	Me	2-Cl-Ph	263-265	MeCN
180	Me	3-Cl-Ph	>300	$CHCl_3$-EtOH
181	Me	4-Cl-Ph	>300	$CHCl_3$-EtOH
182	Me	2-Me-Ph	266-267	MeCN
183	Me	3-Me-Ph	286-287	EtOH
184	Me	4-Me-Ph	>300	EtOH
185	Me	2-MeO-Ph	>300	MeCN
186	Me	3-MeO-Ph	276-278	EtOH
187	Me	4-MeO-Ph	287-289	EtOH
188	Me	2-furyl	>300	EtOH
189	Me	2-thienyl	>300	EtOH
190	Me	3-thienyl	294-295	MeCN
191	Et	Me	259-260	EtOH

Table 19

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
192	Et	n-Pr	202-204	MeCN
193	Et	i-Pr	222-224	MeCN
194	Et	c-Pr	255-257	MeCN
195	Et	n-Bu	196-198	MeCN
196	Et	i-Bu	198-200	MeCN
197	Et	c-hexyl	254-257	MeCN
198	Et	Ph	276-277	EtOH
199	Et	2-F-Ph	242-243	EtOH-i-Pr_2O
200	Et	3-F-Ph	>300	EtOH
201	Et	4-F-Ph	>300	EtOH
202	Et	2-Cl-Ph	260-261	MeCN
203	Et	3-Cl-Ph	>300	$CHCl_3$-MeOH
204	Et	4-Cl-Ph	>300	$CHCl_3$-EtOH
205	Et	2-Me-Ph	245-246	MeCN
206	Et	3-Me-Ph	270-272	MeCN
207	Et	4-Me-Ph	267-269	EtOH
208	Et	2-MeO-Ph	225-226	MeCN
209	Et	3-MeO-Ph	250-252	MeCN
210	Et	4-MeO-Ph	266-268	EtOH
211	Et	2-furyl	254-256	EtOH
212	Et	3-thienyl	286-288	EtOH

Table 20

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
213	Et	4-pyridyl	>300	MeCN
214	n-Pr	Me	217-218	EtOH
215	n-Pr	c-Pr	201-202	MeCN
216	n-Pr	Ph	224-225	EtOH
217	n-Pr	2-F-Ph	220-221	EtOH
218	n-Pr	3-F-Ph	259-261	EtOH
219	n-Pr	4-F-Ph	261-263	EtOH
220	n-Pr	2-furyl	221-223	EtOH
221	n-Pr	2-thienyl	225-227	EtOH
222	n-Pr	3-thienyl	244-246	EtOH
223	i-Pr	Me	244-245	EtOH
224	i-Pr	c-Pr	275-277	MeCN
225	i-Pr	Ph	273-275	MeCN
226	i-Pr	2-F-Ph	257-259	MeCN
227	i-Pr	3-F-Ph	297-299	EtOH
228	i-Pr	4-F-Ph	284-286	EtOH
229	i-Pr	2-furyl	258-260	EtOH
230	i-Pr	2-thienyl	260-262	EtOH
231	i-Pr	3-thienyl	263-264	EtOH
232	c-Pr	Me	251-253	MeCN

Table 21

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
233	c-Pr	i-Pr	224-227	MeCN
234	c-Pr	c-Pr	241-243	MeCN
235	c-Pr	Ph	278-280	EtOH
236	c-Pr	2-F-Ph	219-221	MeCN
237	c-Pr	3-F-Ph	289-291	EtOH
238	c-Pr	4-F-Ph	298-300	EtOH
239	c-Pr	2-Cl-Ph	262-263	MeCN
240	c-Pr	3-Cl-Ph	>300	EtOH
241	c-Pr	4-Cl-Ph	>300	EtOH
242	c-Pr	2-Me-Ph	239-240	MeCN
243	c-Pr	3-Me-Ph	246-248	EtOH
244	c-Pr	4-Me-Ph	>300	EtOH
245	c-Pr	2-furyl	277-278	EtOH
246	c-Pr	2-thienyl	281-282	EtOH
247	c-Pr	3-thienyl	280-281	EtOH
248	n-Pr	3-Cl-Ph	293-295	MeCN
249	i-Pr	3-Cl-Ph	>300	EtOH
250	n-Pr	4-Cl-Ph	287-289	MeCN
251	i-Pr	4-Cl-Ph	>300	EtOH
252	Me	2-Br-Ph	275-278	MeCN
253	Et	2-Br-Ph	254-255	MeCN

Table 22

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
254	c-Pr	2-Br-Ph	259-261	MeCN
255	n-Pr	2-Br-Ph	226-229	MeCN
256	i-Pr	2-Br-Ph	238-239	MeCN
257	Me	3-Br-Ph	>300	$CHCl_3$-EtOH
258	Et	3-Br-Ph	>300	EtOH
259	c-Pr	3-Br-Ph	>300	EtOH
260	n-Pr	3-Br-Ph	>300	EtOH
261	i-Pr	3-Br-Ph	>300	EtOH
262	Me	4-Br-Ph	>300	$CHCl_3$-EtOH
263	Et	4-Br-Ph	>300	MeCN
264	c-Pr	4-Br-Ph	>300	EtOH
265	n-Pr	4-Br-Ph	>300	EtOH
266	i-Pr	4-Br-Ph	>300	EtOH
267	n-Pr	2-Me-Ph	228-230	MeCN
268	i-Pr	2-Me-Ph	223-226	MeCN
269	n-Pr	3-Me-Ph	220-221	MeCN
270	i-Pr	3-Me-Ph	247-249	MeCN
271	n-Pr	4-Me-Ph	252-253	MeCN
272	i-Pr	4-Me-Ph	>300	MeCN
273	Me	2-OH-Ph		

Table 23

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
274	Et	2-OH-Ph		
275	Me	3-OH-Ph		
276	Et	3-OH-Ph		
277	Me	4-OH-Ph		
278	Et	4-OH-Ph		
279	n-Pr	2-MeO-Ph	220-222	MeCN
280	i-Pr	2-MeO-Ph	267-269	MeCN
281	n-Pr	3-MeO-Ph	219-220	MeCN
282	i-Pr	3-MeO-Ph	225-226	MeCN
283	n-Pr	4-MeO-Ph	220-222	MeCN
284	i-Pr	4-MeO-Ph	272-274	MeCN
285	Me	3-CF_3-Ph	>300	EtOH
286	Et	3-CF_3-Ph	>300	EtOH
287	c-Pr	3-CF_3-Ph	288-290	EtOH
288	Me	4-CF_3-Ph	>300	EtOH
289	Me	3-CF_3O-Ph	>300	EtOH
290	Et	3-CF_3O-Ph	293-295	MeCN
291	c-Pr	3-CF_3O-Ph	252-254	MeCN
292	Et	4-CF_3O-Ph	279-281	EtOH
293	c-Pr	4-CF_3O-Ph	279-281	MeCN

Table 24

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
294	Me	n-Pr	242-244	MeCN
295	c-Pr	n-Pr	204-205	MeCN
296	Me	c-Pr	>300	EtOH
297	Ph	Ph	>300	$CHCl_3$-EtOH
298	2-Cl-Ph	Ph	>300	$CHCl_3$-EtOH
299	3-Cl-Ph	Ph	263-265	DMF
300	4-Cl-Ph	Ph	>300	DMF
301	2-Me-Ph	Ph	>300	EtOH
302	3-Me-Ph	Ph	266-267	$CHCl_3$-EtOH
303	4-Me-Ph	Ph	286-287	$CHCl_3$-EtOH
304	2-pyridyl	Ph	>300	EtOH
305	3-pyridyl	Ph	>300	EtOH
306	4-pyridyl	Ph	>300	EtOH
307	2-thienyl	Ph	>300	EtOH

Example 308

Preparation of 3-(5-ethyl-1,3,4-oxadiazol-2-yl)-5-(2-thienyl)-1,6-naphthyridin-2(1H)-one:

(1) A solution of 1,2-dihydro-5-(2-thienyl)-2-oxo-1,6-naphthyridine-3-carboxylic acid (1.36 g) and N,N'-carbonyldimidazole (1.22 g) in DMF (50 ml) was stirred at 70°C for 4 hours. To the solution was added propionylhydrazide (0.53 g), and the mixture was stirred at 70°C for 2 hours. The reaction mixture was concentrated to dryness under reduced pressure, and

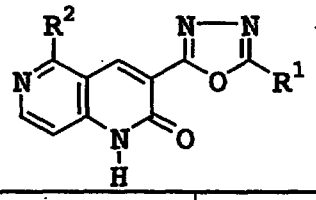
isopropanol was added to the residue, and the precipitated crystals were separated by filtration. The product was washed with isopropanol and diisopropyl ether in this order, and dried to give 1,2-dihydro-N'-propionyl-5-(2-thienyl)-2-oxo-1,6-naphthyridin-3-carbohydrazide (1.21 g) as yellow crystals. This compound was used in the next reaction without being purified.

(2) To a suspension of the above carbohydrazide (1.09 g), triphenylphosphine (1.57 g) and triethylamine (1.06 g) in tetrahydrofuran (THF) (50 ml) was added dropwise diethyl azodicarboxylate (1.04 g) under ice cooling. The mixture was stirred at 70°C for 4 hours. After cooling, water was added to the mixture, and then the mixture was concentrated under reduced pressure, and isopropanol was added to the residue. The precipitated crystals were separated by filtration and dried. The resulting crystals were subjected to silica gel column chromatography and eluted with chloroform-methanol (50 : 1). The crystals were recrystallized from ethanol to give the title compound (0.21 g) as colorless crystals. M.p. >300°C.

Examples 309 to 368

In the same manner as described in Example 308, the corresponding starting materials were reacted to give the compounds of Examples 309 to 368 as shown in Tables 25 to 27.

Table 25



Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
309	Me	Me	>300	MeCN
310	Et	Me	258-259	EtOH
311	Et	Ph	258-259	MeCN
312	n-Pr	Me	209-210	MeCN
313	i-Pr	Me	250-251	EtOH
314	c-Pr	Me	>300	EtOH
315	Me	3-F-Ph	>300	$CHCl_3$-EtOH
316	Et	3-F-Ph	>300	EtOH
317	c-Pr	3-F-Ph	288-290	EtOH
318	n-Pr	3-F-Ph	277-279	EtOH
319	i-Pr	3-F-Ph	241-243	MeCN
320	Me	3-Br-Ph	246-248	EtOH
321	Et	3-Br-Ph	292-293	$CHCl_3$-EtOH
322	c-Pr	3-Br-Ph	>300	MeCN
323	Et	4-Br-Ph	>300	EtOH
324	c-Pr	4-Br-Ph	>300	$CHCl_3$-EtOH
325	c-Pr	2-Me-Ph	283-285	MeCN
326	Me	3-Me-Ph	>300	EtOH
327	Et	3-Me-Ph	258-260	MeCN

Table 26

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
328	c-Pr	3-Me-Ph	244-246	MeCN
329	n-Pr	3-Me-Ph	233-235	MeCN
330	i-Pr	3-Me-Ph	187-189	MeCN
331	Me	4-Me-Ph	>300	$CHCl_3$-EtOH
332	Et	4-Me-Ph	>300	EtOH
333	c-Pr	4-Me-Ph	>300	EtOH
334	n-Pr	4-Me-Ph	>300	EtOH
335	i-Pr	4-Me-Ph	>300	EtOH
336	Me	2-OH-Ph		
337	Et	2-OH-Ph		
338	Me	3-OH-Ph		
339	Et	3-OH-Ph		
340	Me	4-OH-Ph		
341	Et	4-OH-Ph		
342	Et	2-MeO-Ph	267-269	MeCN
343	Me	3-MeO-Ph	>300	EtOH
344	Et	3-MeO-Ph	272-273	MeCN
345	c-Pr	3-MeO-Ph	294-296	MeCN
346	n-Pr	3-MeO-Ph	199-201	MeCN
347	i-Pr	3-MeO-Ph	228-230	MeCN
348	Me	2-thienyl	>300	$CHCl_3$-EtOH
349	c-Pr	2-thienyl	>300	EtOH
350	n-Pr	2-thienyl	292-294	EtOH

Table 27

Ex. No.	R^1	R^2	M.p. (°C)	Solvent for recrystallization
351	i-Pr	2-thienyl	293-296	EtOH
352	Me	Ph	>300	EtOH
353	c-Pr	Ph	>300	MeCN
354	n-Pr	Ph	>300	MeCN
355	n-Bu	Ph	281-283	MeCN
356	c-hexyll	Ph	251-253	MeCN
357	Ph	Ph	>300	DMF
358	2-Cl-Ph	Ph	>300	$CHCl_3$-EtOH
359	3-Cl-Ph	Ph	>300	DMF
360	4-Cl-Ph	Ph	>300	DMF
361	2-Me-Ph	Ph	>300	EtOH
362	3-Me-Ph	Ph	>300	$CHCl_3$-EtOH
363	4-Me-Ph	Ph	>300	$CHCl_3$-EtOH
364	2-pyridyl	Ph	>300	$CHCl_3$-EtOH
365	3-pyridyl	Ph	>300	$CHCl_3$-EtOH
366	4-pyridyl	Ph	>300	$CHCl_3$-EtOH
367	2-thienyl	Ph	>300	$CHCl_3$-EtOH
368	2-furyl	Ph	>300	EtOH

Example 369

Preparation of 1,2-dihydro-5-methyl-2-oxo-1,6-naphthyridine-3-carbonitrile:

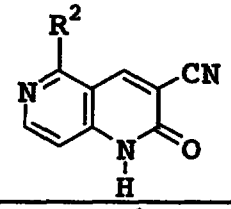
(1) A mixture of acetylacetone (41 ml), N,N-dimethylformamide dimethylacetal (106.2 ml) and THF (200 ml) was stirred at room

temperature for 3 hours. After distilling off the solvent under reduced pressure, the residue was added dropwise to a solution prepared by dissolving metal sodium (13.8 g) in ethanol (600 ml) and adding thereto cyanoacetamide (33.6 g), and the mixture was refluxed for one hour. The reaction mixture was ice-cooled, and the precipitated crystals were separated by filtration. The crystals were dissolved in water (1 liter) and then weakly acidified with 3N hydrochloric acid. The precipitated crystals were separated by filtration and recrystallized from DMF-methanol to give 5-acetyl-6-methyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (60 g) as colorless crystals. M.p. 230°C.

(2) A solution of the above carbonitrile (30 g), N.N-dimethylformamide dimethylacetal (25 ml) and DMF (150 ml) was stirred at room temperature overnight. The precipitated crystals were separated by filtration, washed with methanol and then dried. The crystals thus obtained and ammonium acetate (21.9 g) were added to DMF (300 ml), and the mixture was stirred at 130°C for 3 hours. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, and the resulting crystals were separated by filtration and recrystallized from DMF to give the title compound (Compound No. 1)(25 g) as colorless crystals. M.p. 278°C.

In the same manner as described in Example 369, the corresponding starting materials were reacted to give the compounds of Compound Nos. 2 to 43 as shown in Tables 28 to 29.

Table 28



Comp. No.	R^2	M.p. (°C)
2	H	>290
3	Et	268
4	n-Pr	259
5	i-Pr	283
6	c-Pr	276
7	2-Me-c-Pr	242
8	n-Bu	259
9	i-Bu	236
10	c-Bu	270
11	n-pentyl	265
12	c-hexyl	>290
13	c-hexyl-CH_2	269
14	3-c-hexenyl	>290
15	Ph	>290
16	2-F-Ph	>290
17	3-F-Ph	>290
18	4-F-Ph	>290
19	2-Cl-Ph	>290
20	3-Cl-Ph	>290
21	4-Cl-Ph	>290

Table 29

Comp. No.	R^2	M.p. (°C)
22	2-Br-Ph	291-294
23	3-Br-Ph	280-282
24	4-Br-Ph	
25	2-Me-Ph	>290
26	3-Me-Ph	>290
27	4-Me-Ph	>290
28	2-CF_3-Ph	
29	3-CF_3-Ph	291-294
30	4-CF_3-Ph	>300
31	2-MeO-Ph	289
32	3-MeO-Ph	>290
33	4-MeO-Ph	278
34	3-CF_3O-Ph	264-266
35	4-CF_3O-Ph	>300
36	1-naphthyl	>290
37	2-naphthyl	>290
38	2-furyl	>290
39	2-thienyl	>290
40	5-Cl-2-thienyl	>290
41	3-thienyl	>290
42	3-pyridyl	>290
43	4-pyridyl	285

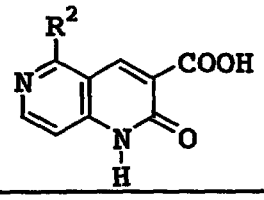
Example 370

Preparation of 1,2-dihydro-5-(2-thienyl)-2-oxo-1,6-naphthyridine-3-carboxylic acid:

A mixture of 1,2-dihydro-5-(2-thienyl)-2-oxo-1,6-naphthyridine-3-carbonitrile (10.0 g), ethanol (300 ml) and 10N NaOH (300 ml) was refluxed overnight. After cooling, the reaction mixture was neutralized with acetic acid, and the precipitated crystals were separated by filtration, washed with water, isopropanol and diisopropyl ether in this order and then dried to give the title compound (Compound No. 44)(10.5 g) as pale yellow crystals. M.p. 278°C.

In the same manner as described in Example 370, the corresponding starting materials were reacted to give the compounds of Compound Nos. 45 to 86 as shown in Tables 30 to 31.

Table 30



Comp. No.	R^2	M.p. (°C)
45	H	246
46	Me	273
47	Et	268
48	n-Pr	>290
49	i-Pr	>290
50	c-Pr	>290
51	2-Me-c-Pr	286
52	n-Bu	248
53	i-Bu	259
54	c-Bu	>290
55	n-pentyl	263
56	c-hexyl	>290
57	c-hexyl-CH_2	>290
58	3-c-hexenyl	>290
59	Ph	>290
60	2-F-Ph	>290
61	3-F-Ph	>290
62	4-F-Ph	>290
63	2-Cl-Ph	>290
64	3-Cl-Ph	>290

Table 31

Comp. No.	R^2	M.p. (°C)
65	4-Cl-Ph	>290
66	2-Br-Ph	288-291
67	3-Br-Ph	>300
68	4-Br-Ph	>300
69	2-Me-Ph	>290
70	3-Me-Ph	>290
71	4-Me-Ph	>290
72	2-CF_3-Ph	
73	3-CF_3-Ph	275-278
74	4-CF_3-Ph	>300
75	2-MeO-Ph	286
76	3-MeO-Ph	>290
77	4-MeO-Ph	>290
78	3-CF_3O-Ph	265-268
79	4-CF_3O-Ph	>300
80	1-naphthyl	>290
81	2-naphthyl	>290
82	2-furyl	>290
83	5-Cl-2-thienyl	>290
84	3-thienyl	>290
85	3-pyridyl	>290
86	4-pyridyl	>290

Preparation 1

Capsules:

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(3-methoxyphenyl)-1,6-naphthyridin-2(1H)-one	5 g
Corn starch	57 g
Lactose	10 g
Crystalline cellulose	25 g
Hydroxypropyl cellulose	2 g
Light silicic anhydride	0.5 g
Magnesium stearate	0.5 g

According to a conventional method, the above components are mixed and kneaded to give the granules, which are packed into 1000 capsules to give a capsule preparation (each 100 mg).

Preparation 2

Tablets:

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(3-methoxyphenyl)-1,6-naphthyridin-2(1H)-one	5 g
Corn starch	20 g
Lactose	30 g
Hydroxypropyl cellulose	5 g
Low-substituted hydroxypropyl cellulose	10 g

According to a conventional method, the above components are mixed and kneaded, and thereto are added light silicic anhydride and magnesium stearate, and the mixture is tabletted to give tablets containing 5 mg of the active ingredient in each

tablet.

Preparation 3

Powder:

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(3-methoxyphenyl)-1,6-naphthyridin-2(1H)-one	5 g
Corn starch	173 g
Lactose	300 g
Hydroxypropyl cellulose	20 g

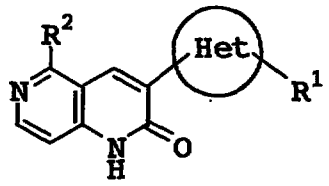
According to a conventional method, the above components are mixed and kneaded, pulverized, and thereto is added light silicic anhydride (q.s.) to give 50-trituration.

INDUSTRIAL APPLICATION

The compounds of this invention have high selective affinity to benzodiazepine receptor and are useful as a drug for acting onto benzodiazepine receptor. Although some of the compounds of this invention have agonistic properties, the compounds of this invention are particularly useful as an inverse agonist. The compounds having inverse agonistic properties are expected to be used in clinical fields entirely different from those of agonists, for example, as psychoanaleptic drug or a drug for the treatment of dysmnesia in senile dementia or Alzheimer's disease.

WHAT IS CLAIMED IS:

1. A 5-substituted-3-oxadiazolyl-1,6-naphthyridin-2(1H)-one derivative having the following formula (I):



(I)

wherein Het is an oxadiazolyl group,

R^1 is a hydrogen atom, a lower alkyl group, a cyclo-lower alkyl group, a trifluoromethyl group, a lower alkenyl group, a lower alkynyl group, a lower alkoxy group, a lower alkoxy-lower alkyl group, a hydroxy-lower alkyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaromatic group, and

R^2 is a hydrogen atom, a lower alkyl group, a cyclo-lower alkyl group, a cyclo-lower alkylmethyl group, a lower alkenyl group, a cyclo-lower alkenyl group, a lower alkynyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaromatic group

or a pharmaceutically acceptable acid addition salt thereof.

2. A 5-substituted-3-oxadiazolyl-1,6-naphthyridin-2(1H)-one derivative according to claim 1, wherein R^1 is a C_1-C_3 alkyl group, a C_3-C_4 cycloalkyl group, or a C_2-C_3 alkenyl group, and R^2 is a hydrogen atom, a C_1-C_4 alkyl group, a C_3-C_6 cycloalkyl group, a substituted or unsubstituted aryl group, or a

substituted or unsubstituted heteroaromatic group, or a pharmaceutically acceptable acid addition salt thereof.

3. A 5-substituted-3-oxadiazolyl-1,6-naphthyridin-2(1H)-one derivative according to claim 1, wherein R^1 is a C_1-C_3 alkyl group or a C_3-C_4 cycloalkyl group and R^2 is a hydrogen atom, a C_1-C_3 alkyl group, a C_3-C_4 cycloalkyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted heteroaromatic group, or a pharmaceutically acceptable acid addition salt thereof.

4. A 5-substituted-3-oxadiazolyl-1,6-naphthyridin-2(1H)-one derivative selected from the following compounds or a pharmaceutically acceptable acid addition salt thereof:

3-(5-Ethyl-1,2,4-oxadiazol-3-yl)-5-(2-methylcyclopropyl)-1,6-naphthyridin-2(1H)-one,

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(2-methylphenyl)-1,6-naphthyridin-2(1H)-one,

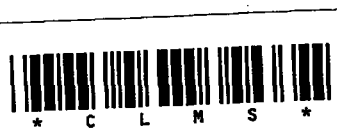
3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(4-methoxyphenyl)-1,6-naphthyridin-2(1H)-one,

3-(5-Ethyl-1,2,4-oxadiazol-3-yl)-5-(2-thienyl)-1,6-naphthyridin-2(1H)-one,

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(4-pyridyl)-1,6-naphthyridin-2(1H)-one,

3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-methyl-1,6-naphthyridin-2(1H)-one,

3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-(3-fluorophenyl)-



1,6-naphthyridin-2(1H)-one,

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-5-(3-methylphenyl)-1,6-naphthyridin-2(1H)-one,

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-5-(3-methoxyphenyl)-1,6-naphthyridin-2(1H)-one,

3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-(4-methoxyphenyl)-1,6-naphthyridin-2(1H)-one,

3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-5-(4-pyridyl)-1,6-naphthyridin-2(1H)-one, and

3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-5-(3-thienyl)-1,6-naphthyridin-2(1H)-one.

5. 3-(5-Methyl-1,2,4-oxadiazol-3-yl)-5-(3-methoxyphenyl)-1,6-naphthyridin-2(1H)-one or a pharmaceutically acceptable acid addition salt thereof.

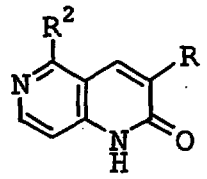
6. A pharmaceutical composition for acting onto benzodiazepine receptor, which comprises the compound as set forth in any one of claims 1 to 5 in admixture with a pharmaceutically acceptable carrier or diluent.

7. A drug for acting onto benzodiazepine receptor, which comprises as an active ingredient the compound as set forth in any one of claims 1 to 5.

This Sheet Has Been Replaced

* C L M S *

8. A 1,6-naphthyridin-2(1H)-one derivative of the formula (I'):



(I')

wherein R is a cyano group, a carbamoyl group, a carboxyl group, a lower alkoxycarbonyl group, or a substituted or unsubstituted benzyloxycarbonyl group, and

R^2 is a lower alkyl group, a cyclo-lower alkyl group, a lower alkenyl group, a cyclo-lower alkenyl group, a lower alkynyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaromatic group, provided that R^2 is not a methyl group or a pyridyl group.