(54) Title: NOVEL ISOQUINOLINE DERIVATIVES

(57) Abstract: The present invention relates to a compound represented by a formula (I): wherein: R is independently from each other a lower alkyl group and the like, X is an oxygen atom or a sulfur atom, Y is a lower alkylene group having 1 to 6 carbon atoms, R<sup>1</sup> is a phenyl group and the like which may be substituted by a halogen atom and the like, and any CH<sub>2</sub> in the following: (1-1) may be substituted by a lower alkyl group, and R<sup>2</sup> is a phenyl group or a pyridinyl group which may be substituted by a lower alkyl group and the like, m is 0, 1, 2 or 3, and n is 0 or 1, or a pharmaceutically acceptable salt thereof.
NOVEL ISOQUINOLINE DERIVATIVES

TECHNICAL FIELD

The present invention relates to isoquinoline derivatives useful in the pharmaceutical field. The compound of the present invention acts as a GPR131 receptor function regulator, especially as a GPR131 agonist, and is useful as agents for treating and/or preventing diabetes, obesity and hyperlipidemia.

BACKGROUND OF ART

A GPR131 which is a G protein-coupled receptor transmits a signal into a cell via binding to bile acid such as lithocholic acid whereby inducing various in vivo reactions. The effects of the GPR131 and its ligand are reported, in an intestinal tract cell line, to promote the secretion of a GLP-I (glucagon-like-peptide-1) which serves to reduce blood glucose level (see Non-patent document 1). The GLP-I is a peptide hormone released by an L cell which is an intestinal secreting cell present in ileum, large intestine and the like, and was demonstrated to induce insulin secretion depending on blood glucose level. Accordingly, a compound having a GLP-I secretion-promoting effect is expected to be used as a therapeutic agent for diabetes which can avoid a risk of hypoglycemia due to overdose. In addition, since the GLP-I has an ability of inducing pancreatic β cell proliferation and its differentiation from stem cells (see Non-patent document 2), it is suggested to be effective in delaying apoptosis of β cells in Type II diabetes and in sustaining the effect of islet implantation in Type I diabetes.

The GPR131 is known to be expressed also in a skeletal muscle. This organ is very important in energy consumption. A D2 gene (type 2 iodothyronine deiodinase: an enzyme required to convert a thyroid hormone into its active form in cells) is also expressed in the skeletal muscle. An increase in cAMP concentration due to activation of the GPR131 is known to serve to activate the D2 (see Non-patent document 3), thus having an energy metabolism-stimulating effect. Thus, an anti-obesity effect of a novel mechanism can be expected when utilizing the GPR131 agonistic effect to increase the concentration of an active form thyroid hormone in an
organ critical in the energy consumption whereby increasing the energy consumption.

Based on the above description, a compound having a GPR13 agonistic activity is considered to be very useful as a therapeutic or prophylactic agent for diabetes and obesity.

As compounds related structurally to the compounds according to the present invention, those represented by following formula:

were reported (see Patent document 1). The nitrogen atom forming an amide bond in these compounds is NH, while a compound according to the invention is substituted by a group other than H. Furthermore, a biphenyl is bound to the NH constituting an amide group, while no biphenyl group is contained in the compound according to the invention. Moreover, although the compound described in Patent document 1 has a Factor Xa inhibiting effect and is reported to be useful in treating a thrombosis, usefulness of these compounds in treating and/or preventing diabetes, obesity and hyperlipidemia is not described or even suggested.

Also as G protein-coupled receptor kinase inhibitors having isoquinoline skeleton, the compounds represented by following formula:

were reported (see Patent document 2). Although these compounds have isoquinoline skeleton, said isoquinoline backbones have NH-C(O) groups attached directly thereto, which, together with other groups, are different from the compounds according to the invention. In addition, the uses of the compounds described in Patent document 2 is for glaucoma and the like, and usefulness of these compounds in treating and/or preventing diabetes, obesity and hyperlipidemia is not described or even suggested.

patent document 1: WO2002/024654 Publication
Non-patent document 1: Biochemical and biophysical research


DISCLOSURE OF INVENTION

An objective of the present invention is to provide a novel isoquinoline derivative having a GPR131 agonistic effect.

We made an effort to develop a compound having a GPR131 function regulatory effect, especially an agonistic effect, and finally found that a compound according to the invention is effective as a compound having a GPR131 function regulatory effect, especially an agonistic effect, and based on such findings the present invention was accomplished.

Thus, the invention relates to a compound represented by a formula (I):

\[
\begin{align*}
\text{R}^1 &\quad \text{is selected from a group consisting of a lower alkyl group, a lower alkoxy group and a halogen atom;} \\
X &\quad \text{is an oxygen atom or a sulfur atom;} \\
Y &\quad \text{is a lower alkylene group;} \\
\text{R}^1 &\quad \text{is a group selected from a group consisting of a phenyl group, a pyridinyl group, an isoquinolinyl group and a naphthalenyl group;} \\
\text{said R}^1 &\quad \text{is optionally substituted with 1 to 3, same or different groups selected from a group consisting of a halogen atom, a lower alkyl group optionally substituted with 1 to 3, same or different halogen atoms, a lower alkoxy group optionally substituted with 1 to 3, same or different halogen atoms, a nitro group, an alkanoyl group, a cyano group, a carbamoyl group, a mono- or di-lower alkylcarbamoyl group,}
\end{align*}
\]

or a pharmaceutically acceptable salt thereof, wherein:
and a lower alkylsulfonyl group;

any CH₂ in the following:

\[
\begin{array}{c}
\text{R}^2 \\
\end{array}
\]

is optionally substituted with a lower alkyl group;

\( R^2 \) is a group selected from a group consisting of:

1. a phenyl group or a pyridinyl group optionally with 1 to 3, same or different substituents selected from a group consisting of a lower alkyl group optionally substituted with 1 to 3, same or different halogen atoms, a lower alkoxy group optionally substituted with 1 to 3, same or different halogen atoms, and a halogen atom;

2. a cycloalkyl group having 3 to 7 carbon atoms;

said cycloalkyl group is optionally fused with a benzene ring, or may form an aliphatic heterocyclic ring in which one of the carbon atoms constituting said cycloalkyl group is replaced with an oxygen atom or a nitrogen atom, and when one of the carbon atoms constituting said cycloalkyl group is replaced with a nitrogen atom, then said nitrogen atom is optionally substituted with a group selected from a group consisting of a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkoxy carbonyl group, a lower alkylsulfonyl group, a lower alkyl group optionally substituted with 1 to 3, same or different halogen atoms, an alkanoyl group and a lower alkoxyalkyl group; and,

3. a lower alkyl group optionally substituted with 1 to 3, same or different halogen atoms;

m is 0, 1, 2, or 3;

n is 0 or 1.

The invention also relates to a GPR13 agonist regulating agent containing the compound represented by the formula (I) or the pharmaceutically acceptable salt thereof as an active ingredient, and especially the invention relates to a GPR13 agonist containing as an active ingredient the compound represented by the formula (I) or the pharmaceutically acceptable salt thereof.

The invention also relates to an agent for treating and/or preventing diabetes, obesity and/or hyperlipidemia containing as an active ingredient the compound represented by the formula (I) or the pharmaceutically acceptable salt thereof.
The invention also relates to a pharmaceutical composition containing the compound represented by the formula (I) and a pharmaceutically acceptable carrier.

The compound (I) according to the invention and the pharmaceutically acceptable salt thereof have a potent GPR13 function regulating effect, especially an agonistic effect, and are useful in treating and/or preventing diabetes, obesity or hyperlipidemia.

The followings are definitions of terms employed in the specification and describe the compounds according to the invention in more detail.

A "halogen atom" includes, for example a fluorine atom, a chlorine atom, a bromine atom, an iodine atom and the like.

A "lower alkyl group" means a straight or branched alkyl group having 1 to 6 carbon atoms, such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a s-butyl group, a t-butyl group, a pentyl group, an isoamyl group, a neopentyl group, an isopentyl group, a 1,1-dimethylpropyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,2-dimethylpropyl group, a hexyl group, an isohexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 1,1-dimethylbutyl group, a 1,2-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,3-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,2,2-trimethylpropyl group, a 1-ethyl-2-methylpropyl group and the like.

A "lower alkoxy group" means a group in which a hydrogen atom of the hydroxy group is substituted by a lower alkyl group described above, for example, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, a s-butoxy group, a t-butoxy group, a pentyloxy group, an isopentyloxy group, a hexyloxy group, an isohexyloxy group and the like.

Each symbol employed in the formula (I):

\[
\begin{align*}
\text{(I)} & \\
\end{align*}
\]
is described specifically below.

Each R is independently selected from the group consisting of a lower alkyl group, a lower alkoxy group, and a halogen atom.

A "lower alkyl group" represented by R includes, for example a group similar to the lower alkyl group defined above, and specifically includes a methyl group, an ethyl group, a n-propyl group, an isopropyl group and the like.

A "lower alkoxy group" represented by R includes, for example be a group similar to the lower alkoxy group defined above, and specifically includes a methoxy group, an ethoxy group, a n-propoxy group, an isoproxy group and the like.

A "halogen atom" represented by R includes, for example an atom similar to the halogen atom defined above, and specifically includes a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom.

The "lower alkyl group" and the "lower alkoxy group" represented by R are each substituted with 1 to 3, same or different halogen atoms.

Such a "halogen atom" of the substituent includes, for example an atom similar to the halogen atom defined above, and specifically includes a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom.

X is an oxygen atom or a sulfur atom.

X is preferably an oxygen atom.

Y is a lower alkylene group having 1 to 4 carbon atoms.

A "lower alkylene group having 1 to 6 carbon atoms" represented by Y means a straight or branched lower alkylene group having 1 to 6 carbon atom, and specifically includes a methylene group, an ethylene group, a propylene group, a tetramethylene group, a methyldimethylene group, a dimethyldimethylene group, a methylethylene group, a 1,1-dimethylethylene group, or a 1,2-dimethylethylene group and the like.

Y is preferably a methylene group.

R\text{\textasciitilde} is a group selected from the group consisting of a phenyl group, a pyridinyl group, an isoquinolinyl group and a naphthalenyl group.

Said R\text{\textasciitilde} is optionally substituted with 1 to 3, same or different groups selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted with 1 to 3 same or different halogen atoms, a lower alkoxy group optionally substituted with 1 to 3 same or different halogen atoms, a nitro group, an
alkanoyl group, a cyano group, a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, and a lower alkylsulfonyl group.

Such a "halogen atom" of the substituent means an atom similar to the halogen atom defined above, and specifically includes a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom.

Said "lower alkyl group" of the substituent means a group similar to the lower alkyl group defined above, and specifically includes a methyl group, an ethyl group, a n-propyl group, an isopropyl group and the like.

Said lower alkyl group of the substituent may be substituted with 1 to 3 same or different halogen atoms defined above.

Said "lower alkoxy group" of the substituent means a group similar to the lower alkoxy group defined above, and specifically includes a methoxy group, an ethoxy group, a n-propoxy group, an isoproxy group and the like.

Said lower alkoxy group of the substituent is optionally substituted with 1 to 3 same or different halogen atoms defined above.

Said "alkanoyl group" of the substituent includes, for example anacetyl group, an ethylcarbonyl group and the like.

Said "mono-lower alkylcarbamoyl group" of the substituent means a carbamoyl group substituted by a lower alkyl group defined above, and includes, for example a methylcarbamoyl group, an ethylcarbamoyl group, a n-propylcarbamoyl group, isopropylcarbamoyl group and the like.

Said "di-lower alkylcarbamoyl group" of the substituent means a carbamoyl group di-substituted by said same or different lower alkyl groups defined above, and includes, for example a dimethylcarbamoyl group, an ethylmethylcarbamoyl group, a diethylcarbamoyl group, diisopropylcarbamoyl group and the like.

Said "lower alkylsulfonyl group" of the substituent means a sulfonyl group bound to a lower alkyl group defined above, and includes, for example a methylsulfonyl group, an ethylsulfonyl group, a n-propylsulfonyl group, isopropylsulfonyl group and the like.

R\(^1\) is preferably a phenyl group or a pyrindinyl group.

Said phenyl group or pyridinyl group optionally substituted with 1 to 3, same or different groups selected from the group consisting of a halogen atom, a lower alkyl group optionally substituted with 1 to 3 same or different halogen atoms,
a lower alkoxy group optionally substituted with 1 to 3 same or different halogen atoms, a nitro group, an alkanoyl group, a cyano group, a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, and a lower alkylsulfonyl group.

R$^1$ is preferably a group selected from the group consisting of a formula (II-1):

![Chemical Structures](image)

and more preferable is a group selected from a group consisting of the formula (II-1):
wherein the following:

indicates the position of binding to a nitrogen atom.

In the formula (I), any CH₂ in the following group:

(II-2)

(wherein n is 0 or 1) is optionally substituted with a lower alkyl group.

Said "lower alkyl group" of the substituent means a group similar to the lower alkyl group defined above, and includes for example a methyl group, an ethyl group, a n-propyl group, an isopropyl group and the like.

R² is a group selected from the group consisting of:

(1) a phenyl group or a pyridinyl group optionally substituted with 1 to 3 groups selected from a group consisting of a lower alkyl group optionally substituted with 1 to 3, same or different halogen atoms, a lower alkoxy group optionally substituted with 1 to 3, same or different halogen atoms, and a halogen atom;

(2) a cycloalkyl group having 3 to 7 carbon atoms; said cycloalkyl group may be fused with a benzene ring, or may form an aliphatic heterocyclic ring in which one of the carbon atoms constituting said cycloalkyl group is replaced with an oxygen atom or a nitrogen atom, and when one of the carbon atoms constituting said cycloalkyl group is replaced with a nitrogen atom, then said nitrogen atom may be
substituted by a group selected from a group consisting of a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkoxy carbonyl group, a lower alkylsulfonyl group, a lower alkyl group which may be mono- to tri-substituted by 1 to 3 same or different halogen atoms, an alkanoyl group and a lower alkoxyalkyl group); and,

(3) a lower alkyl group optionally substituted with 1 to 3, same or different halogen atoms.

The phenyl group or pyridinyl group represented by \( R^2 \) is optionally substituted with 1 to 3 groups selected from a group consisting of a lower alkyl group, a lower alkoxy group, and a halogen atom.

Said "lower alkyl group" of the substituent means a group similar to the lower alkyl group defined above, and includes for example a methyl group, an ethyl group, a n-propyl group, an isopropyl group and the like.

Said lower alkyl group of the substituent is optionally substituted with 1 to 3 same or different halogen atoms defined above.

Said "lower alkoxy group" of the substituent means a group similar to the lower alkoxy group defined above, and includes for example a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group and the like.

Said lower alkoxy group of the substituent is optionally substituted with 1 to 3 same or different halogen atoms defined above.

Said "halogen atom" of the substituent means a group similar to the halogen atom defined above.

Said "cycloalkyl group having 3 to 7 carbon atoms" represented by \( R^2 \) includes, for example, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group or a cycloheptyl group.

Said cycloalkyl group having 3 to 7 carbon atoms may be fused with a benzene ring.

Such a group fused with a benzene ring includes, for example, a 2-indanyl group and the like.

Said cycloalkyl group having 3 to 7 carbon atoms may form an aliphatic heterocyclic ring in which one of the carbon atoms constituting said cycloalkyl group is replaced with an oxygen atom or a nitrogen atom.

Such an aliphatic heterocyclic ring includes, for example, a tetrahydropyranyl
group, a tetrahydrofuranyl group, an azetidinyl group, a piperidinyl group, a pyrrolidinyl group, a hexametyleniminyl group and the like.

When said aliphatic heterocyclic ring underwent the replacement of one of the carbon atoms constituting said cycloalkyl group by a nitrogen atom, then said nitrogen atom is optionally substituted with a group selected from the group consisting of a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkoxy carbonyl group, a lower alkyl group, an alkanoyl group and a lower alkoxyalkyl group.

Said mono-lower alkylcarbamoyl group of the substituent means a carbamoyl group mono-substituted with a lower alkyl group defined above, and includes for example an ethylcarbamoyl group, a methylcarbamoyl group, a n-propylcarbamoyl group, isopropyl carbamoyl group and the like.

Said di-lower alkylcarbamoyl group of the substituent means a carbamoyl group di-substituted by same or different lower alkyl groups defined above, and includes for example a diethylcarbamoyl group, a dimethylcarbamoyl group, an ethylmethyl carbamoyl group, diisopropylcarbamoyl group and the like.

Said lower alkoxy carbonyl group of the substituent means a carbonyl group bound to the lower alkoxy group defined above, and includes for example a methoxycarbonyl group, an ethoxycarbonyl group, a n-propoxycarbonyl group, an isoproxy carbonyl group, t-butoxycarbonyl group and the like.

Said lower alkyl group of the substituent means a group similar to the lower alkyl group defined above, and includes for example a methyl group, an ethyl group, a n-propyl group, an isopropyl group and the like.

Said alkanoyl group of the substituent includes for example an acetyl group, an ethylcarbonyl group and the like.

Said lower alkoxyalkyl group of the substituent includes for example a methoxymethyl group, a methoxyethyl group, an ethoxymethyl group, an ethoxyethyl group, an isoproxy methyl group and the like.

A "lower alkyl group" represented by $R^2$ includes for example a group similar to the lower alkyl group defined above, and specifically includes a methyl group, an ethyl group, a n-propyl group, an isopropyl group and the like.

A "lower alkyl group" represented by $R^2$ is optionally substituted with 1 to 3 same or different halogen atoms defined above.
Said "halogen atom" of the substituent means an atom similar to the halogen atom defined above, and includes for example a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom.

Preferably, \(R^2\) is a group selected from the group consisting of:

1. a phenyl group or a pyridinyl group optionally substituted with 1 to 3 same or different halogen atoms,
2-a. a cyclopropyl group, a cyclobutyl group, a cyclopentyl group or a cyclohexyl group,
2-b. a group wherein one of carbon atoms constituting a cycloalkyl group having 3 to 7 carbon atoms is replaced by a nitrogen atom, wherein a substituent on said nitrogen atom is a group selected from the group consisting of a lower alkoxy carbonyl group, an alkanoyl group, a lower alkyl group, a lower alkylsulfonyl group, a mono- or di-lower alkyl carbamoyl group, and a lower alkoxyalkyl group, and,
3. a lower alkyl group.

In the case where \(R^2\) is:

1. a phenyl group or a pyridinyl group optionally substituted with 1 to 3 same or different halogen atoms,
as described above, \(R^2\) is more preferably a group represented by the following:

\[
\begin{align*}
&\text{phenyl} &\text{F} &\text{F} &\text{Cl} &\text{pyridinyl} \\
&\text{phenyl} &\text{F} &\text{F} &\text{Cl} &\text{pyridinyl}
\end{align*}
\]

wherein the following:

\[
\begin{align*}
&\text{indicates the position of binding to a nitrogen atom.}
\end{align*}
\]

Alternatively, in the case where \(R^2\) is:

2-b. a group wherein one of carbon atoms constituting a cycloalkyl group having 3 to 7 carbon atoms is replaced by a nitrogen atom, wherein a substituent on said nitrogen atom is a group selected from the group consisting of a lower alkoxy carbonyl group, an alkanoyl group, a lower alkyl group, a lower alkylsulfonyl group, a mono- or di-lower alkyl carbamoyl group, and a lower alkoxyalkyl group, as described above, \(R^2\) is more preferably a group represented by the following:
wherein $R_3$ is a group selected from the group consisting of a lower alkoxy carbonyl group, an alkanoyl group, a lower alkyl group, a lower alkylsulfonyl group, a mono- or di-lower alkylcarbamoyl group, and a lower alkoxyalkyl group, and $p$ and $q$ are each independently 1 or 2, and,

the following:

\[ \text{---} \]

indicates the position of binding to a nitrogen atom, and, further preferably a group selected from the group represented by the following:

\[ \text{---} \]

indicates the position of binding to a nitrogen atom.

$m$ is 0, 1, 2 or 3.

$n$ is 0, or 1.

The compounds according to the present invention represented by the formula (I) includes for example, but are not limited to, the followings:

N-(2-chloro-4-fluorophenyl)-N-(1-ethylpropyl)-2-(5-isoquinolinyloxy)acetamide,

N-(2-chloro-4-fluorophenyl)-2-(5-isoquinolinyloxy)-N-methylacetamide,

N-(2-chloro-4-fluorophenyl)-N-cyclopropyl-2-(5-isoquinolinyloxy)acetamide,

N-(2-chloro-4-fluorophenyl)-N-cyclopentyl-2-(5-isoquinolinyloxy)acetamide,
N-(2-chloro-4-fluorophenyl)-N-cyclopentyl-2-(5-isoquinolinyloxy)2-methylpropanamide,
4-{(2-chloro-4-fluorophenyl)\[(5-isoquinolinyloxy)acetyl]amino]-N,N-dimethyl-l-piperidine carboxamide,
N-(2-chloro-4-fluorophenyl)-2-(5-isoquinolinyloxy)-N-(1-phenylethyl)acetamide,
N-(2-chloro-4-fluorophenyl)-N-(2-cyano-4-fluorophenyl)-2-(5-isoquinolinyloxy)acetamide,
N-(2-cyano-4-fluorophenyl)-N-(4-fluorophenyl)-2-(5-isoquinolinyloxy)acetamide,
N-(2-chloro-4-fluorophenyl)-2-(5-isoquinolinyloxy)-N-4-pyridinylacetamide, or,
2-(5-isoquinolinyloxy)-N,N-diphenylacetamide.

Methods for producing compounds according to the invention are described below.

A compound (1-1) of the present invention:

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^{21} \\
\text{Y} & \quad \text{X}
\end{align*}
\]

(1-1)

wherein:

R\text{21} is a cycloalkyl group having 3 to 7 carbon atoms (said cycloalkyl group is optionally fused with a benzene ring, or may form an aliphatic heterocyclic ring in which one of the carbon atoms constituting said cycloalkyl group is replaced by an oxygen atom or a nitrogen atom, and when one of the carbon atoms constituting said cycloalkyl group is replaced by a nitrogen atom, then said nitrogen atom is optionally substituted with a group selected from the group consisting of a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, a lower alkoxy carbonyl group, a lower alkylsulfonfyl group, a lower alkyl group optionally substituted with 1 to 3 same or different halogen atoms, an alkanoyl group and a lower alkoxyalkyl group), or a lower alkyl group optionally substituted with 1 to 3 same or different halogen atoms, and other symbols are as described above, can be produced for example by the following methods.
wherein:

$L_1$ and $L_2$ are leaving groups, and other symbols are as described above.

(Step 1)

This step is a method for producing a compound (3) by reacting a compound (1) and a compound (2) in the presence of a reducing agent.

The compound (2) means an aldehyde compound or a ketone compound.

The amount of the compound (2) employed is usually 1 to 5 equivalents, preferably, 1 to 2 equivalents relative to 1 equivalent of the compound (1).

Reducing agents employed includes for example sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride and the like, with triacetoxyborohydride being preferred.

The amount of such a reducing agent is usually 1 to 10 equivalents, preferably, 1 to 3 equivalents relative to 1 equivalent of the compound (1).

It is also possible to add additives such as anhydrous sodium sulfate, acetic acid, zinc chloride and the like to the reaction system.

The reaction time is usually 10 minutes to 48 hours, preferably 10 minutes to 24 hours.

The reaction temperature is usually 0 to 100°C, preferably 0 to 50°C.

Reaction solvents employed in this step may be any one of those having no adverse effect on the reaction, including for example methanol, ethanol, chloroform, methylene chloride, THF, 1,4-dioxane.

When using acetic acid and the like in the reaction system, such an acetic acid and the like may be used as a reaction solvent.

The compound (3) thus obtained can be isolated and purified in a known
separation and purification method, for example, concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, chromatography, or may be subjected to the next step without isolation or purification.

(Step 2)

This step is a method for producing a compound (5) by reacting the compound (3) and a compound (4) in the presence of a base.

Bases employed includes for example triethylamine, diisopropylethylamine, potassium carbonate, sodium carbonate, cesium carbonate and the like.

The amount of such a base is usually 1 to 10 equivalents, preferably, 1 to 3 equivalents relative to 1 equivalent of the compound (1).

The amount of the compound (4) employed is usually 1 to 20 equivalents, preferably, 1 to 5 equivalents relative to 1 equivalent of the compound (3).

$L_1$ and $L_2$ of the compound (4) include for example chlorine atom, bromine atom and the like.

The reaction time is usually 1 to 24 hours, preferably 1 to 5 hours.

The reaction temperature is usually 0 to 200°C, preferably 20 to 100°C.

Reaction solvents employed in this step may be any one of those having no adverse effect on the reaction, including for example toluene, tetrahydrofuran (also referred to as THF), DMF(N,N-dimethyl formamide), DMA(N,N-dimethylacetamide), chloroform, N-methylpyrrolidone (also referred to as NMP) and the like.

The compound (5) thus obtained can be isolated and purified in a known separation and purification method, for example, concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, chromatography or may be subjected to the next step without isolation or purification.

(Step 3)

This step is a method for producing a compound (1-1) according to the invention by reacting the compound (5) and a compound (6) in the presence of a base.

Bases employed include for example triethylamine, diisopropylethylamine, potassium carbonate, sodium carbonate, cesium carbonate and the like.

The amount of such a base is usually 1 to 10 equivalents, preferably, 1 to 5 equivalents relative to 1 equivalent of the compound (5).

The amount of the compound (6) employed is usually 1 to 5 equivalents, preferably, 1 to 3 equivalents relative to 1 equivalent of the compound (5).
The reaction time is usually 1 to 24 hours, preferably 1 to 5 hours.
The reaction temperature is usually 0 to 150°C, preferably 20 to 50°C.
Reaction solvents employed in this step may be any one of those having no adverse effect on the reaction, and include for example THF, DMF, DMA, chloroform, NMP.

The compound (1-1) thus obtained can be isolated and purified in a known separation and purification method, for example concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, chromatography.

A compound (1-2) according to the invention:

\[
\begin{align*}
&\text{can be produced for example by the following methods:}

\text{Step 4} & \quad \text{(1)} \xrightarrow{\text{R}^{22}-L_3} \text{(7)} \quad \text{Step 4} \quad \text{(8)} \quad \text{Step 5} \quad \text{(9)} \quad \text{Step 6} \\
&\text{wherein } L_3 \text{ is a leaving group, } R^{22} \text{ is a phenyl group or a pyridinyl group optionally substituted with 1 to 3 same or different halogen atoms.}

\text{(Step 4)}

\text{This step is a method for producing a compound (8) by reacting the compound (1) and the compound (7) in the presence of a base.}

\text{Bases employed includes for example sodium hydride, potassium t-butoxide.}

\text{The amount of such a base is usually 1 to 10 equivalents, preferably, 1 to 3 equivalents relative to 1 equivalent of the compound (1).}

\text{The amount of the compound (7) employed is usually 1 to 5 equivalents,}
preferably, 1 to 3 equivalents relative to 1 equivalent of the compound (1). The reaction time is usually 1 to 24 hours, preferably 1 to 5 hours. The reaction temperature is usually 0 to 50°C, preferably 0 to 20°C. Reaction solvents employed in this step may be any one of those having no adverse effect on the reaction, and include for example THF, DMF, DMA, NMP.

The compound (8) thus obtained can be isolated and purified in a known separation and purification method, for example, concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, chromatography, or may be subjected to the next step without isolation or purification.

(Step 5)

This step is a method for producing a compound (9) by reacting the compound (8) and the compound (4). In order to promote the reaction in this step, a base may be added to the reaction system.

Such a base includes for example triethylamine, diisopropylamine, sodium carbonate, potassium carbonate, cesium carbonate and the like. The amount of such a base is usually 1 to 10 equivalents, preferably, 1 to 3 equivalents relative to 1 equivalent of the compound (8).

Also in order to promote the reaction in this step, the reaction system may be subjected to a microwave reactor. The reaction time is usually 1 to 24 hours, preferably 1 to 5 hours. The reaction temperature is usually 20 to 200°C, preferably 50 to 100°C. Reaction solvents employed in this step may be any one of those having no adverse effect on the reaction, and include for example NMP, DMF, DMA, THF.

The compound (9) thus obtained can be isolated and purified in a known separation and purification method, for example concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, chromatography, or may be subjected to the next step without isolation or purification.

(Step 6)

This step is a method for producing a compound (1-2) according to the invention by reacting the compound (9) and the compound (6) in the presence of a base.

Bases employed includes for example triethylamine, diisopropylamine,
potassium carbonate, sodium carbonate, cesium carbonate.

The amount of such a base is usually 1 to 5 equivalents, preferably, 1 to 3 equivalents relative to 1 equivalent of the compound (9).

The amount of the compound (6) employed is usually 1 to 5 equivalents, preferably, 1 to 3 equivalents relative to 1 equivalent of the compound (9).

The reaction time is usually 1 to 48 hours, preferably 1 to 5 hours.

The reaction temperature is usually 0 to 100°C, preferably 20 to 50°C.

Reaction solvents employed in this step may be any one of those having no adverse effect on the reaction, and include for example DMF, DMA, NMP.

The compound (1-2) thus obtained can be isolated and purified in a known separation and purification method, for example concentration, concentration under reduced pressure, reprecipitation, solvent extraction, crystallization, chromatography.


A compound according to the invention can exist as a pharmaceutically acceptable salt, and said salt can be produced according to a standard method using the compounds represented by the formula (I) described above and the formulae (1-1) and (1-2) encompassed therein.

The acid-addition salts include, for example, hydrohalides such as hydrochlorides, hydrofluorides, hydrobromides, hydroiodides; inorganic acid salts such as nitrates, perchlorates, sulfates, phosphates, carbonates; lower alkylsulfonates such as methanesulfonates, trifluoromethanesulfonates, ethanesulfonates; arylsulfonates such as benzenesulfonates, p-toluenesulfonates; organic acid salts such as fumarates, succinates, citrates, tartrates, oxalates, maleates; other organic acid-addition salts with amino acid such as glutamates, aspartates.

When the compounds of the invention have an acid group in the molecule, for example, when they have a carboxyl group, then the compounds may be processed with a base so as to convert them into the corresponding pharmaceutically-acceptable salts.

The base-addition salts include, for example, alkali metal salts with sodium or potassium; alkaline earth metal salts with calcium or magnesium;
ammonium salts; organic base-addition salts with guanidine, triethylamine, dicyclohexylamine, etc.

In addition, the compounds of the invention may also be in any other form of hydrates or solvates of their free compounds or their salts.

Conversely, conversion from a salt or an ester into a free compound may also be accomplished according to a standard method.

Depending on the type of the substituents therein, the compounds of the invention include stereoisomers and tautomers such as optical isomers, diastereomeric isomers and geometrical isomers. Needless-to-say, the compounds of the invention include all these isomers. Further needless-to-say, the compounds of the invention include all mixtures of such isomers.

In producing medicines for prevention and remedy for type II diabetes or diseases or symptoms associated with it, the compounds of the formula (I) of the invention may be combined with carrier substances.

The dose of the compounds of the formula (I) of the invention for prevention or remedy for diseases naturally varies, depending on the property of the symptom to which the treatment is directed, the specific compound selected for it and the administration route.

In addition, the dose also varies depending on the age, the body weight and the sensitivity of patients. In general, the daily dose for one-time or plural-times administration may be from about 0.001 mg/kg-body weight to about 100 mg/kg-body weight, preferably from about 0.01 mg/kg-body weight to about 50 mg/kg-body weight, even more preferably from about 0.1 mg/kg-body weight to about 10 mg/kg-body weight. As the case may be, administration of a dose over the range may be necessary.

An example of a suitable dose for oral administration is described. The daily dose for one-time or two- to four-times administration may be at least from about 0.01 mg to at most 2.0 g. Preferably, the daily administration frequency is once or twice a day, and the daily dose is from about 1.0 mg to about 200 mg. More preferably, the daily dose is from about 10 mg to 100 mg for one-time administration a day.

For intravenous administration or oral administration, a typical dose of the compound (I) may be from about 0.001 mg/day/kg-body weight to about 100
mg/day/kg-body weight (preferably from 0.01 mg/day/kg-body weight to about 10
mg/day/kg-body weight), more preferably from about 0.1 mg/day/kg-body weight to
10 mg/day/kg-body weight.

As so mentioned hereinabove, a pharmaceutical composition of the
invention comprises the compound of the formula (I) and a pharmaceutically-
acceptable carrier. The term "composition" is meant to contain not only a product
produced by directly or indirectly combining, hybridizing or aggregating 2 or more
ingredients, a product produced as a result of dissociation of one or more ingredients,
or a compound produced as a result of reaction or interaction of different types of
ingredients, but also an active and inactive ingredient of constituting a carrier
(pharmaceutically-acceptable vehicle).

As combined with the pharmaceutically-acceptable carrier, the
composition of the invention preferably contains the compound of the formula (I) in
an amount effective for remedy and prevention of type II diabetes and for retardation
of the onset of the disease.

For administering the effective dose of the compound of the invention
to mammals, especially to humans, employable is any suitable administration route.
For example, the route may be oral administration, rectal administration, local
administration, intravenous administration, ophthalmic administration, lung
administration or nasal administration. Examples of the administration forms are
tablets, troches, powders, suspensions, solutions, capsules, creams, aerosols.
Preferred are oral tablets.

In preparing oral compositions, usable are any ordinary pharmaceutical
media. Their examples are water, glycol, oil, alcohol, fragrant additives,
preservatives, colorants. In preparing liquid compositions for oral administration,
for example, mentioned are suspensions, elixirs and solutions. Their carriers are,
for example, starch, sugar, microcrystalline cellulose, diluent, granulating promoter,
lubricant, binder, disintegrator. In preparing solid compositions for oral
administration, for example, mentioned are powders, capsules and tablets. Above all,
such solid compositions for oral administration are preferred.

In view of the easiness in their administration, tablets and capsules are
the most advantageous forms for oral administration. If desired, the tablets may be
coated according to standard aqueous or non-aqueous coating techniques.
In addition to the above-mentioned ordinary administration modes for them, the compounds of the formula (I) may also be administered according to controlled release systems and/or controlled delivery systems, for example, as in US Patents 3,845,770, 3,916,899, 3,536,809, 3,598,123, 3,630,200 and 4,008,719.

The pharmaceutical composition of the invention suitable for oral administration includes capsules, cashews and tablets that contain a predetermined amount of the active ingredient in the form of powders or granules thereof, or in the form of water-soluble liquids, water-insoluble liquids, oil-in-water emulsions or water-in-oil emulsions thereof. These compositions may be prepared in any pharmaceutical methods, and all the methods include a process of combining the active ingredient with a carrier of one or more necessary ingredients.

In general, the active ingredient is uniformly and fully mixed with a liquid carrier, or a well-separated solid carrier or with both the two, and then, if desired, the product is shaped into suitable forms to prepare the composition. For example, tablets are produced through compression and shaping, optionally along with one or more side components. Using a suitable machine, compressed tablets may be produced by mixing the active ingredient optionally with binder, lubricant, inert vehicle, surfactant or dispersant and compressing the resulting mix in any desired manner into powders or granules.

Shaped tablets may be prepared by shaping a mixture of a powdery wet compound and an inert liquid diluent, using a suitable machine.

Preferably, the tablets each contain from about 1 mg to 1 g of the active ingredient; and the cashews and the capsules each contain from about 1 mg to 500 mg of the active ingredient.

Examples of the administration modes of the compounds of the formula (I) for pharmaceutical use are as follows:
Table 1

<table>
<thead>
<tr>
<th>Suspension for Injection (I. M.)</th>
<th>mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of formula (I)</td>
<td>10</td>
</tr>
<tr>
<td>methyl cellulose</td>
<td>5.0</td>
</tr>
<tr>
<td>Tween 80</td>
<td>0.5</td>
</tr>
<tr>
<td>benzyl alcohol</td>
<td>9.0</td>
</tr>
<tr>
<td>benzalkonium chloride</td>
<td>1.0</td>
</tr>
<tr>
<td>water for injection added to make 1.0 ml</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Tablets</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of formula (I)</td>
<td>25</td>
</tr>
<tr>
<td>methyl cellulose</td>
<td>415</td>
</tr>
<tr>
<td>Tween 80</td>
<td>14.0</td>
</tr>
<tr>
<td>benzyl alcohol</td>
<td>43.5</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>500 mg</strong></td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Capsules</th>
<th>mg/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of formula (I)</td>
<td>25</td>
</tr>
<tr>
<td>lactose powder</td>
<td>573.5</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>600 mg</strong></td>
</tr>
</tbody>
</table>
The compounds of the formula (I) may be used, as combined with any other drugs usable not only for type II diabetes-associated diseases or symptoms but also for remedy/prevention/retardation of the onset of type II diabetes. The additional drugs may be administered in any administration route and dose generally employed in the art, simultaneously with or separately from the compound of the formula (I).

In case where the compound of the formula (I) is used along with one or more other drugs, then a pharmaceutical composition comprising the compound of the formula (I) and the additional drug is preferred. Accordingly, the pharmaceutical composition of the invention may comprise not only the compound of the formula (I) but also one or more such active ingredients. Examples of the active ingredients that may be combined with the compounds of the formula (I) are mentioned below, which, however, are not limitative. These may be separately administered or may be administered simultaneously as contained in the same pharmaceutical composition.

(a) other GPR120 agonists
(b) glucokinase activators,
(c) bis-guanides (e.g., buformin, metoformin, fenformin),
(d) PPAR agonists (e.g., triglytazon, pioglytazon, nosiglytazon),
(e) insulin,
(f) somatostatin,
(g) α-glucosidase inhibitors (e.g., boglybose, miglytol, acarbose),
(h) insulin secretion promoters (e.g., acetohexamide, calbutamide, chlorpropamide, glybomlide, glycrazide, glymerpiride, glypidide, glyquidine, glysoxepide, glyburide, glyhexamide, glypinamide, fenbutamide, trazamide, tolbutamide, tolclyclamide, nateglynide, repaglynide),
(i) DPP-IV (dipeptidyl peptidase IV) inhibitors, and

The weight ratio of the compound of the formula (I) to the second active ingredient may vary within a broad range, and depends on the effective amount of the individual active ingredients. Accordingly, for example, when the compound of the formula (I) is combined with a PPAR agonist, then the weight ratio of the compound of the formula (I) to the PPAR agonist may be generally from about 1000/1 to 1/1000, preferably from about 200/1 to 1/200. The combination of the compound of the formula (I) and the other active ingredient may be within the above-mentioned range. In any case, an effective amount of the individual ingredients should be in the combination.

While a compound according to the invention has GPR120 function regulating effect, the "GPR120 function regulating effect" herein means that the function of the GPR120 receptor is activated or inhibited and a GPR120 agonist is included in those having GPR120 function regulating effects.

EXAMPLES

Formulation 1

The invention is further detailed below referring to formulations, Examples, and Comparatives, which are not intended to restrict the invention.

10 Parts of the compound of Example 1, 15 parts of heavy magnesium oxide and 75 parts of lactose are mixed uniformly to form a pulverized or particulate powder whose particle size is 350 μm or less. This powder is filled in a capsule blank to obtain a capsule formulation.

Formulation 2

45 Parts of the compound of Example 1, 15 parts of starch, 16 parts of a lactose, 21 parts of a crystalline cellulose, 3 parts of a polyvinyl alcohol and 30 parts of a distilled water are mixed uniformly, pulverized and granulated, dried, and then sieved to form a granule formulation whose particle size is 1410 to 177 μm.

Formulation 3

A granule formulation is produced similarly to formulation 2, and then 96 parts of this granule formulation is combined with 3 parts of a calcium stearate, and compressed to form a tablet whose diameter is 10 mm.
Formulation 4

90 parts of a granule formulation produced similarly to formulation 2 is combined with 10 parts of a crystalline cellulose and 3 parts of a calcium stearate, and compressed to form a tablet whose diameter is 8 mm, which is combined with a suspension mixture of a syrup gelatin and a sedimented calcium carbonate to form a sugar-coated tablet.

In Examples, the silica gel column chromatography employed a column prepacked with Wakogel (trade mark, Wako Pure Chemical) C-300 or KP-SiI (trade mark) Silica from Biotage. The preparative chromatography employed a Kieselgel™60F₂₅₄, Art. 5744 from Merck. The basic silica gel chromatography employed Chromatorex (trade mark) NH (100 to 250 mesh or 200 to 350 mesh) from Fiji Silicia Chemical.

A ¹H-NMR was obtained using JEOL AL400 (400 MHz), Mercury (400 MHz), Inova (400 MHz), together with a tetramethysilane as a reference standard. A mass spectrum was obtained by an electrospray ionization method (ESI) or an atmospheric pressure chemical ionization method (APCI) using a Waters micromass ZQ.

The following abbreviations are used in Examples described below.

i-Bu: Isobutyl group
n-Bu: n-Butyl group
t-Bu: tert-Butyl group
Boc: tert-Butoxycarbonyl group
Me: Methyl group
Et: Ethyl group
Ph: Phenyl group
i-Pr: Isopropyl group
n-Pr: n-Propyl group
CDCI₃: Heavy chloroform
CD₃OD: Heavy methanol
DMSO-d₆: Heavy dimethyl sulfoxide

The meanings of abbreviations in a nuclear magnetic resonance spectrometry are shown below.

s: Singlet
d: Doublet
dd: Double doublet
dt: Double triplet
ddd: Double double triplet
Sept: Septet
t: Triplet
m: Multiplet
br: Broad
brs: Broad singlet
q: Quartet
J: Coupling constant
Hz: Hertz

Example 1

**Synthesis of N-(2-chloro-4-fluorophenyl-N-(1-ethylpropyl)-2-(5-isoquinolinyloxy)acetamide**

![Chemical structure](image)

1) 2-Chloro-N-(1-ethylpropyl)-4-fluoroaniline

To a solution of 2-Chloro-4-fluoroaniline (728 mg) in acetic acid (25 ml) was added 3-pentanone (862 mg) and anhydrous sodium sulfate (7.10 g), and the solution was stirred for 20 minutes at room temperature. To the reaction solution was added sodium triacetoxyborohydride (3.18 g) and the solution was stirred for 3 hours at room temperature. The reaction solution was poured into a saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic phase was washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resultant residue was purified by a silica gel chromatography (hexane:ethyl acetate=40:1 to 20:1) to obtain the title compound (1.03 g) as a colorless oil.

2) 2-Chloro-N-(2-chloro-4-fluorophenyl-N-(1-ethylpropyl)acetamide

To a solution of the compound (1.03 g) obtained in Step 1) in toluene (10 ml) was added chloroacetyl chloride (807 mg), and the solution was stirred for 2.5 hours
at 100°C. The reaction solution was poured into a saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic phase was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resultant residue was purified by a silica gel chromatography (hexane:ethyl acetate=10: 1 to 5:1) to obtain the title compound (1.25 g) as a colorless oil.

3) N-(2-chloro-4-fluorophenyl)-N-(1-ethylpropyl)-2-(5-isoquinolinyloxy)acetamide

To a solution the compound (1.25 g) obtained in Step 2 in dimethyl formamide (40ml) was added 5-isoquinolinol (745 mg) and cesium carbonate (4.18 g), and the solution was stirred for 6 hours at 60°C. To the reaction solution was added water and the reaction solution was extracted with ethyl acetate. The organic phase was washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resultant residue was purified by a silica gel chromatography (hexane:ethyl acetate=5: 1 to 1:1) to obtain the title compound (743 mg) as a yellow oil.

H-NMR(CDCl₃)δ:0.92(3H,t,J=7.6Hz),0.98(3H,t,J=7.3Hz),1.10-1.21(1H,m), 1.39-1.51(1 H,m), 1.67-1.83(2H,m),4.49-
4.56(1H,m),4.57(1H,d,J=14.6Hz),4.62(1H,d,J=15.1Hz),6.90(1H,d,J=7.8Hz),6.96(1H,d,
dd,J=9.6,7.0,2. 1Hz),7. 12(1H,dd,J=8.8,5.4Hz),7.32(1H,dd,J=7.8,2.9Hz),7.44(1H,t,J=8.
0Hz),7.54(1H,d,J=8.3Hz),7.82(1H,d,J=5.9Hz)8.49(1H,d,J=5.9Hz),9. 18(1H,d,J=1 .0Hz)
ESI-MS(m/e):40 1.1[M+H]⁺

Example 2

Synthesis of N-(2-chloro-4-fluorophenyl)-2-(5-isoquinolinyloxy)-N-methylacetamide

The title compound was obtained as a yellow solid using 2-chloro-4-fluoro-N-methylaniline by the method similar to that in Example 1, methods analogous thereto, or standard method combined therewith.

H-
NMR (CDCl$_3$) $\delta$: 3.26 (3H, s), 4.58 (1H, d, J = 14.6 Hz), 4.64 (1H, d, J = 14.6 Hz), 6.90 (1H, d, J = 7.3 Hz), 7.00-7.05 (1H, m), 7.27-7.30 (2H, m), 7.46 (1H, d, J = 8.0 Hz), 7.57 (1H, d, J = 8.3 Hz), 7.89 (1H, d, J = 6.3 Hz), 8.50 (1H, d, J = 6.3 Hz), 9.20 (1H, d, J = 8.0 Hz)

ESI-MS (m/e): 345.0 [M+H]$^+$

Example 3

**Synthesis of N-(2-chloro-4-fluorophenyl)-N-cyclopropy-2-(5-isoquinolinyloxy)acetamide**

The title compound was obtained as a yellow oil using 2-chloro-N-cyclopropyl-4-fluoroaniline by the method similar to that in Example 1, methods analogous thereto, or standard method combined therewith.

$^1$H-NMR (CDCl$_3$) $\delta$: 0.51-0.59 (1.4H, m), 0.73-0.88 (2H, m), 0.92-1.01 (0.6H, m), 3.23-3.29 (1H, m), 4.51 (0.7H, d, J = 5.1 Hz), 4.56 (0.7H, d, J = 15.1 Hz), 5.29 (0.6H, s), 6.86 (0.7H, d, J = 7.3 Hz), 6.99-7.04 (1.3H, m), 7.12 (1H, d, J = 8.5, 5.6 Hz), 7.21-7.23 (0.3H, m), 7.29 (0.7H, dd, J = 7.8, 2.4 Hz), 7.44 (0.7H, t, J = 8.0 Hz), 7.48-7.61 (1.3H, m), 7.90 (0.7H, d, J = 5.9 Hz), 8.13 (0.3H, d, J = 5.9 Hz), 8.54 (0.3H, d, J = 5.9 Hz), 9.19 (0.7H, s), 9.22 (0.3H, s)

ESI-MS (m/e): 371.0 [M+H]$^+$

Example 4

**Synthesis of N-(2-chloro-4-fluorophenyl)-N-cyclopentyl-2-(5-isoquinolinyloxy)acetamide**

The title compound was obtained as a pale yellow solid using 2-chloro-N-
cyclopentyl-4-fluoroaniline by the method similar to that in Example 1, methods analogous thereto, or standard method combined therewith.

\[1 \text{H-NMR(CDC}_3\text{)} \delta: 1.18-1.30(1H,m), 1.40-1.49(1H,m), 1.50-1.65(4H,m), 1.78-2.00(1H,m), 2.05-2.15(1H,m), 4.49(2H,s), 6.88(1H,d,J=7.3Hz), 7.04(1H,ddd,J=9.4,6.7,2.1Hz), 7.45(1H,d,J=8.2Hz), 7.49(1H,ddd,J=8.0,2.7Hz), 7.56(1H,d,J=8.8Hz), 7.97(1H,d,J=5.9Hz), 8.50(1H,d,J=5.9Hz), 9.20(1H,s)\]

ESI-MS(m/e):399.0[M+H]

Example 5

Synthesis of N-(2-chloro-4-fluorophenyl)-N-cyclopentyl-2-(5-isoquinolinyloxy)-2-methylpropanamide

To a solution of 2-(5-isoquinolinyloxy)-2-methylpropanoic acid in thionyl chloride (200 ml) was added dimethylformamide (50 µl) and the solution was stirred for 1.5 hours at 100°C. The reaction solution was concentrated under reduced pressure to obtain 2-(5-isoquinolinyloxy)-2-methylpropanoyl chloride as a crude product. To a toluene solution (5 ml) of the resultant acid chloride (150 mg) was added 2-chloro-N-cyclopentyl-4-fluoroaniline (56 mg) and the solution was stirred for 4 hours at 100°C. The reaction solution was poured into a saturated aqueous solution of sodium hydrogen carbonate, and extracted with ethyl acetate. The organic phase was washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resultant residue was purified by a silica gel chromatography (hexane:ethyl acetate=2:1 to 1:2) to obtain the title compound (15 mg) as a colorless oil.

\[1 \text{H-NMR(CDC}_3\text{)} \delta: 0.96-1.13(2.5H,m), 1.27-1.33(2.5H,m), 1.43-1.48(1.5H,m), 1.53(1.5H,s), 1.68(1.5H,s), 1.71-1.77(1H,m), 1.84(1.5H,s), 2.00(1.5H,s), 2.15-2.21(0.5H,m), 4.62-4.70(0.5H,m), 5.16-5.24(0.5H,m), 6.36-6.41(0.5H,m), 6.47(0.5H,d,J=8.3Hz, 8.5.9Hz), 6.88-6.92(0.5H,m), 6.97-
Example 6

Synthesis of 4-[(2-chloro-4-fluorophenyl)(5-isoquinolinyloxy)acetyl]amino)-N,N-dimethyl-1-piperidine carboxamide

The title compound was obtained as a colorless oil using 4-[(2-chloro-4-fluorophenyl)amino]-N,N-dimethyl-1-piperidine carboxamide by the method similar to that in Example 1, methods analogous thereto, or standard method combined therewith.

1H-NMR(CDCl₃)δ:1.16-1.27(IH,m), 1.44-1.54(IH,m), 1.88-2.02(2H,m), 2.76(6H,s), 2.81-2.90(2H,m), 3.65-3.76(2H,m), 4.49(1H,d,J=1.5Hz), 4.54(1H,d,J=1.5Hz), 4.69-4.77(1H,m), 5.1Hz), 6.86(1H,d,J=7.3Hz), 7.03(1H,ddd,J=9.5,6.8,2.0Hz), 7.18(1H,dd,J=8.8,5.4Hz), 7.34(1H,dd,J=7.8,2.9Hz), 7.44(1H,t,J=8.0Hz), 7.55(1H,d,J=8.3Hz), 7.91(1H,d,J=5.9Hz), 8.51(1H,d,J=6.3Hz), 9.19(1H,d,J=1.0Hz)

ESI-MS(m/e):485. 1[M+H]⁺

Example 7

Synthesis of N-(2-chloro-4-fluorophenyl)-2-(5-isoquinolinyloxy)-N-(l-phenylethyl)acetamide
The title compound was obtained as a pale orange solid using 2-chloro-4-fluoro-N-(1-phenylethyl)aniline by the method similar to that in Example 1, methods analogous thereto, or standard method combined therewith.

\[ \text{H}^1 \text{NMR(CDCl}_3\text{)} \delta: 1.43(2.2H,d,J=7.3Hz), 1.66(0.8H,d,J=7.3Hz), 4.48(1.3H,d,J=15.1Hz), 4.60(0.7H,d,J=15.1Hz), 6.00(0.3H,q,J=7.8 Hz), 6.23(0.7H,dd,J=8.8,5.4Hz), 6.35(0.7H,dd J=14.6,7.3Hz), 6.69-6.73(0.7H,brs), 6.85(0.5H,brs), 7.05-7.33(3.4H,m), 7.44(1H,td,J=7.9,2.3Hz), 7.56(1H,t,J=8.0Hz), 7.69(0.5H,d,J=8.3Hz), 7.87(0.5H,d,J=5.9Hz), 8.11(0.5H,d,J=5.9Hz), 8.47-8.52(1.5H,brs), 8.63(0.5H,d,J=5.9Hz), 9.7(0.5H,brs), 9.19(1H,d,J=4.4Hz), 29(0.5H,s)\]

ESI-MS(m/e):435.0[M+H]

Example 8

Synthesis of N-(2-chloro-4-fluorophenyl)\( \pi \)-N-(2-cyano-4-fluorophenyl)\( \pi \)-2-(5-isooquinolinyloxy)acetamide

1) 2-{Y2-chloro-4-fluorophenyl)amino1-5-fluorobenzonitrile

To a solution of 2-chloro-4-fluoroaniline (3.07 g) in N-methyl-2-pyrrolidone (40ml) was added potassium t-butoxide (4.97 g), the solution was stirred for 10 minutes, added 2,5-difluorobenzonitrile (3.26 g) in N-methyl-2-pyrrolidone (4ml), and then the solution was stirred for 4 hours at room temperature. While cooling on ice, water was added and then extraction was conducted with ethyl acetate. The organic phase was washed with water and a saturated aqueous sodium chloride
solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant residue was purified by a silica gel chromatography (hexane:chloroform=6:1 to 1:1) to obtain an orange solid, which was washed with hexane (40 ml) to obtain the title compound (2.62 g) as a pale orange solid.

2) 2-chloro-N-(2-chloro-4-fluorophenyl)-N-(2-cyano-4-fluorophenyl)acetamide

A chloroacetyl chloride solution (14 ml) of the compound (700 mg) obtained in Step 1) was stirred for 1 hour at 150°C in a microwave reactor. The resultant residue was purified by a silica gel chromatography (hexane:ethyl acetate=4:1) to obtain the title compound (864 mg) as a tan oil.

3) N-(2-chloro-4-fluorophenyl)-N-(2-cyano-4-fluorophenyl)-2-(5-isoquinolinyloxy)acetamide

To a solution of the compound (845 mg) obtained in Step 2) in dimethyl formamide (5 ml) was added 5-hydroxyisoquinoline (479 mg) and potassium carbonate (514 mg), and the solution was stirred for 15 hour at room temperature. While cooling on ice, water was added and then extraction was conducted with ethyl acetate. The organic phase was washed with water and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant residue was purified by a silica gel chromatography (hexane:ethyl acetate=1:1 to 1:3) to obtain the title compound (603 mg) as a colorless solid.

$^1$H-NMR(CDCl$_3$) $\delta$: 4.90 (1H,d,J=15 Hz), 4.95 (1H,d,J=15 Hz), 6.98 (1H,t,J=7.3Hz), 7.09 (1H,d,J=7.3Hz), 7.28-7.33 (2H,m), 7.40-7.47 (2H,m), 7.5 (1H,q,J=7.6Hz), 7.58 (1H,d,J=7.8Hz), 7.79 (1H,d,J=5.4Hz), 8.49 (1H,d,J=5.9Hz), 9.19 (1H,s)

ESI-MS(m/e):450.0[M+H] +

Example 9
Synthesis of N-(2-cyano-4-fluorophenyl)-N-(4-fluorophenyl)-2-(5-isoquinolinyloxy)acetamide
The title compound was obtained as a pale yellow solid using 5-fluoro-2-[(4-fluorophenyl)amino]benzonitrile by the method similar to that in Example 8, methods analogous thereto, or standard method combined therewith.

\[ \text{ESI-MS (m/e): 416.1 [M+H]^+} \]

Example 10

**Synthesis of N-(2-chloro-4-fluorophenyl)-2-(5-isoquinolinyloxy)-N-4-pyridinylacetamide**

The title compound was obtained as a colorless oil using N-(2-chloro-4-fluorophenyl)-4-pyridineamine by the method similar to that in Example 8, methods analogous thereto, or standard method combined therewith.

\[ \text{ESI-MS (m/e): 408.1 [M+H]^+} \]

Example 11

**Synthesis of 2-(5-JSQUJnOlJnVlOXv)-N.N-diphenylacetamide**
The title compound was obtained as a colorless oil using N-phenylaniline by the method similar to that in Example 8, methods analogous thereto, or standard method combined therewith.

\[ \delta:4.83(2H,s),6.93(1H,d,J=7.8Hz),7.29-7.31(6H,m),7.38(4H,brs),7.47(1H,t,J=8.0Hz),7.57(1H,d,J=8.3Hz),7.88(1H,d,J=5.9Hz),8.49(1H,d,J=5.9Hz),9.19(1H,s) \]

ESI-MS (m/e): 355.2 [M+H]⁺

The usefulness of a compound encompassed by formula (1) as a pharmaceutical can be verified for example in the following Experiments.

Evaluation of the usefulness of a compound according to the invention was conducted by an in vitro assay described below.

**Experiment 1: Gene cloning**

Primers were synthesized from the regions before and after the base sequence of an ORF of GPR13₁, which is a known GPCR in GenBank Accession No.NM_001077 194 (human) and No.NM_174985 (mouse), and an RT-PCR was conducted to clone the gene. The primers employed had the following base sequences.

hGPR13₁_F12: CCCCTGTCCCCAGGACCAAGATG (SEQ.ID.No. 1)

hGPR13₁_R15: TTAGTTCAAGTCCAGGTCGACACTGCTTT (SEQ.ID.No.2)

mGPR13₁_F12: GTGCCAAGACCATGATGACACCC (SEQ.ID.No.3)

mGPR13₁_R13: CTAAATCCAGTGCAATGCTGC (SEQ.ID.No.4)

A human fetus marathon-ready cDNA (CLONTECH: presently TaKaRa) as a human GPR13₁ receptor gene and a cDMA reverse-transcribed from a mouse BAT tissue-derived RNA as a mouse GPR13₁ receptor were employed as samples in the PCR.

The PCR involved amplification using 94°C for 9 minutes followed by 94°C for 30 seconds and then 68°C for 3 minutes which were repeated for 26 cycles in AmpliTaq Gold (Roche). The PCR products thus amplified were cloned using pCR2. 1-TOPOTA cloning kit (Invitrogen). Verification of the base sequences were
based on the base sequencing after electrophoresis using BigDye Terminator Cycle Sequencing Ready Reaction Kit ver. 3.0 and DNA sequencer 377 (Applied Biosynthesis). The GPR13 1 receptor gene cloned into a pCR2.1-TOPO vector was cut out from the vector using a restriction enzyme BamHI and EcoRV, and then subcloned into the BamHI and EcoRI recognition sites in an eukaryotic expression vector pIREShyg3 (clontech).

**Experiment 2: Expression cell production**

Using LIPOFECTAMINE (Invitrogen), the cDNA of the GPR13 1 receptor was transfected to HEK/CRE-BLA cells, from which drug-resistant cells were isolated to obtain cell lines exhibiting stable expression of the GPR13 1. The HEK cells expressing the GPR13 1 were cultured in a DMEM/F12 medium containing 10% fetal bovine serum, 100 units/mL penicillin, 0.1 mg/mL streptomycin sulfate, 250 µg/mL Hygromycin.

**Experiment 3: Intracellular cAMP content assay**

On the day of the measurement, 10,000 human GPR13 1-expressing HEK cells in each well of a 384-well plate (Coning) were exposed to a test compound in the presence of 100 µM Ro-20-1724, and assayed for the intracellular cAMP content by HitHunter XS+ kit (Discoverx), whereby examining the agonistic effects.

The GPR13 1 agonistic effects of the group of the compounds included in the compounds of the present invention were demonstrated as described below.

**[Table 5]**

<table>
<thead>
<tr>
<th>Example</th>
<th>Co.No.</th>
<th>EC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>19.7</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>36.8</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>63.5</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>40.5</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>7.37</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>11.7</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>488</td>
</tr>
</tbody>
</table>

Based on the results shown above, the compounds of the present invention have the GPR13 1 agonistic effects, and are useful in treating and/or preventing diabetes, obesity, and hyperlipidemia.
CLAIMS

1. A compound of a formula (I):

\[
\begin{array}{c}
\text{R}^1 \quad \text{N} \quad \text{Y} \quad \text{X} \quad \text{R}^m \\
\text{O} \quad \text{m}
\end{array}
\]  

(I)

, or a pharmaceutically acceptable salt thereof:

wherein:

each \( R \) is independently selected from a group consisting of a lower alkyl group optionally substituted with 1 to 3 same or different halogen atoms, a lower alkoxy group optionally substituted with 1 to 3 same or different halogen atoms, and a halogen atom;

\( X \) is an oxygen atom or a sulfur atom;

\( Y \) is a lower alkyylene group having 1 to 6 carbon atoms;

\( \text{R}^1 \) is a group selected from a group consisting of a phenyl group, a pyridinyl group, an isoquinolinyl group and a naphthalenyl group;

said \( \text{R}^1 \) is optionally substituted with 1 to 3 same or different substituents selected from a group consisting of a halogen atom, a lower alkyl group optionally substituted with 1 to 3 same or different halogen atoms, a lower alkoxy group optionally substituted with 1 to 3 same or different halogen atoms, a nitro group, an alkanoyl group, a cyano group, a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, and a lower alkylsulfonyl group;

any \( \text{CH}_2 \) in the following:

\[
\begin{array}{c}
(\quad) \\
\text{n}
\end{array}
\]

is optionally substituted with a lower alkyl group;

\( \text{R}^2 \) is a group selected from a group consisting of:

(1) a phenyl group or a pyridinyl group optionally substituted with 1 to 3, same or different substituents selected from a group consisting of a lower alkyl group optionally substituted with 1 to 3, same or different halogen atoms, a lower alkoxy group optionally substituted with 1 to 3 same or different halogen atoms, and a
halogen atom;

(2) a cycloalkyl group having 3 to 7 carbon atoms;
said cycloalkyl group is optionally fused with a benzene ring, or may form an
cycloalkyl group is replaced with an oxygen atom or a nitrogen atom, and when one
of the carbon atoms constituting said cycloalkyl group is replaced with a nitrogen
atom, then said nitrogen atom is optionally substituted with a group selected from a
group consisting of a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, a
lower alkoxy carbonyl group, a lower alkylsulfonyl group, a lower alkyl group
optionally substituted with 1 to 3, same or different halogen atoms, an alkanoyl group
and a lower alkoxyalkyl group; and,

(3) a lower alkyl group optionally substituted with 1 to 3, same or different
halogen atoms;
m is 0, 1, 2, or 3;
n is 0 or 1.

2. The compound according to Claim 1 wherein X is an oxygen atom; Y
is methylene, or the pharmaceutically acceptable salt thereof.

3. The compound according to Claim 2 wherein R² is a group selected
from a group consisting of a phenyl group and a pyridinyl group
optionally substituted with 1 to 3, same or different substituents selected from the
group consisting of a halogen atom, a lower alkyl group optionally substituted with 1
to 3, same or different halogen atoms, a lower alkoxy group optionally substituted
with 1 to 3, same or different halogen atoms, a nitro group, an alkanoyl group, a
cyano group, a carbamoyl group, a mono- or di-lower alkylcarbamoyl group, and a
lower alkylsulfonyl group, or the pharmaceutically acceptable salt thereof.

4. The compound according to Claim 3 wherein R² is a group selected
from the group consisting of:
(1) a phenyl group or a pyridinyl group;
said phenyl group or pyridinyl group is optionally substituted with 1 to 3,
same or different halogen atoms,
(2-a) a cyclopropyl group, a cyclobutyl group, a cyclopentyl group or a cyclohexyl
group;
each of these groups may be taken together with a benzene ring to form a
fused ring,
(2-b) a group wherein one of carbon atoms constituting a cycloalkyl group having 3 to 7 carbon atoms is replaced by a nitrogen atom, wherein a substituent on said nitrogen atom is a group selected from a group consisting of a lower alkoxy carbonyl group, an alkanoyl group, a lower alkyl group, a lower alkylsulfonyl group, a mono- or di-lower alkylcarbamoyl group, and a lower alkoxyalkyl group, and,
(3) a lower alkyl group,
or the pharmaceutically acceptable salt thereof.

5. The compound according to Claim 3 wherein \( R^2 \) is a phenyl group or a pyridinyl group;
said phenyl group or pyridinyl group is optionally substituted with 1 to 3, same or different halogen atoms, or the pharmaceutically acceptable salt thereof.

6. The compound according to Claim 3 wherein \( R^2 \) is a cyclopropyl group, a cyclobutyl group, a cyclopentyl group or a cyclohexyl group or the pharmaceutically acceptable salt thereof.

7. The compound according to Claim 3 wherein \( R^2 \) is a group wherein one of carbon atoms constituting a cycloalkyl group having 3 to 7 carbon atoms is replaced by a nitrogen atom, wherein a substituent on said nitrogen atom is a group selected from the group consisting of a lower alkoxy carbonyl group, an alkanoyl group, a lower alkyl group, a lower alkylsulfonyl group, a mono- or di-lower alkylcarbamoyl group, and a lower alkoxyalkyl group or the pharmaceutically acceptable salt thereof.

8. The compound according to Claim 3 wherein \( R^2 \) is a lower alkyl group or the pharmaceutically acceptable salt thereof.

9. The compound according to Claim 3 wherein \( R^1 \) is a group selected from the group consisting of formula (II-l):
wherein the following:

indicates the position of binding to a nitrogen atom or the pharmaceutically acceptable salt thereof.

10. The compound according to Claim 3 wherein \( R^1 \) is a group selected from a group consisting of a formula (II-2):
wherein the following:

indicates the position of binding to a nitrogen atom or the pharmaceutically acceptable salt thereof.

11. The compound according to Claim 7 wherein \( R^2 \) is the following:

\[
\begin{align*}
& \text{wherein } R^3 \text{ is a group selected from a group consisting of a lower alkoxy carbonyl group, an alkanoyl group, a lower alkyl group, a} \\
& \text{lower alkylsulfonyl group, a mono-} \\
& \text{or di-lower carbamoyl group, and a lower alkoxyalkyl group, and } p \text{ and } q \text{ are} \\
& \text{independently from each other 1 or 2, and,}
\end{align*}
\]

indicates the position of binding to a nitrogen atom or the pharmaceutically acceptable salt thereof.

12. The compound according to Claim 11 wherein \( R^2 \) is a group selected from the group consisting of the following:
13. The compound according to Claim 8 wherein \( R^2 \) is a group selected from the group consisting of a methyl group, an ethyl group, an n-propyl group, and an isopropyl group or the pharmaceutically acceptable salt thereof.

14. The compound according to Claim 1 wherein the compound represented by the formula (I) is:

- \( \text{N-}(2\text{-chloro-4-fluorophenyl})\text{-N-}(1\text{-ethylpropyl})\text{-2-(5-isoquinolinyloxy)acetamide} \)
- \( \text{N-}(2\text{-chloro-4-fluorophenyl})\text{-2-(5-isoquinolinyloxy)}\text{-N-methylacetamide} \)
- \( \text{N-}(2\text{-chloro-4-fluorophenyl})\text{-N-cyclopropyl-2-(5-isoquinolinyloxy)acetamide} \)
- \( \text{N-}(2\text{-chloro-4-fluorophenyl})\text{-N-cyclopentyl-2-(5-isoquinolinyloxy)acetamide} \)
- \( \text{N-}(2\text{-chloro-4-fluorophenyl})\text{-N-cyclopentyl-2-(5-isoquinolinyloxy)2-methylpropanamide} \)
- \( 4\text{-}(2\text{-chloro-4-fluorophenyl})\text{[(5-isoquinolinyloxy)acetyl]amino}\text{-N,N-dimethyl-l-piperidine carboxamide} \)
- \( \text{N-}(2\text{-chloro-4-fluorophenyl})\text{-2-(5-isoquinolinyloxy)}\text{-N-(1-phenylethyl)acetamide} \)
- \( \text{N-}(2\text{-chloro-4-fluorophenyl})\text{-N-(2-cyano-4-fluorophenyl)-2-(5-isoquinolinyloxy)acetamide} \)
- \( \text{N-}(2\text{-cyano-4-fluorophenyl})\text{-N-(4-fluorophenyl)-2-(5-isoquinolinyloxy)acetamide} \)
- \( \text{N-}(2\text{-chloro-4-fluorophenyl})\text{-2-(5-isoquinolinyloxy)}\text{-N-4-pyridinylacetamide} \)
- \( 2\text{-}(5\text{-isoquinolinyloxy)}\text{-N,N-diphenylacetamide} \) or the pharmaceutically acceptable salt thereof.
15. A GPR13 agonist containing the compound according to any one of claims 1 to 14 or the pharmaceutically acceptable salt thereof as an active ingredient.

16. A therapeutic and/or prophylactic agent for hyperlipidemia, diabetes and/or obesity containing the compound according to any one of claims 1 to 14 or the pharmaceutically acceptable salt thereof as an active ingredient.

17. A pharmaceutical composition containing the compound according to any one of claims 1 to 14 and a pharmaceutically acceptable carrier.
## INTERNATIONAL SEARCH REPORT

### A CLASSIFICATION OF SUBJECT MATTER

Int.Cl See extra sheet

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)


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

- Published examined utility model applications of Japan 1922-1996
- Published unexamined utility model applications of Japan 1971-2010
- Published registered utility model applications of Japan 1994-2010

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

C/plus/REGI STRY (STN)

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex

Date of the actual completion of the international search: 07.05.2010

Date of mailing of the international search report: 18.05.2010

Name and mailing address of the ISA/JP Patent Office: 3-4-3, Kasumigaseki, CMyoda-ku, Tokyo 100-8915, Japan

Authorized officer: Kiyoko TAMURA

Telephone No. +81-3-3581-1 101 Ext. 3492

Form PCT/ISA/210 (second sheet) (July 2009)
CLASSIFICATION OF SUBJECT MATTER
C07D217/24 (2006. 01) i, A61K31/472 (2006. 01) i, A61K31/4725 (2006. 01) i,
A61P3/04 (2006. 01) i, A61P3/06 (2006. 01) i, A61P3/10 (2006. 01) i,
A61P43/00 (2006. 01) i, C07D401/12 (2006. 01) i