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(54) Title: NOVEL INHIBITORS OF DPP-IV, METHODS OF PREPARING THE SAME, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME AS AN ACTIVE AGENT

(57) Abstract: The present invention relates to pyrroolidine-based compounds of novel structure exhibiting good inhibitory activity versus Dipeptidyl Peptidase-IV, as defined in Formula 1 of the specification, and methods of preparing the same and pharmaceutical compositions containing the same as an active agent.

[Continued on next page]
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Description

Novel inhibitors of DPP-IV, Methods Of Preparing The Same, And Pharmaceutical Compositions Containing The Same As An Active Agent

Technical Field

The present invention relates to pyrrolidine-based compounds of novel structure, having good inhibition activity versus Dipeptidyl Peptidase-IV (DPP-IV), methods of preparing the same and pharmaceutical compositions containing the same as an active agent.

Background Art

Diabetes mellitus has serious effects on people's health and accompanies various complications. There are two major types of diabetes mellitus: type I diabetes mellitus characterized by little or no insulin secretory capacity due to the destruction of pancreatic cells, and type II diabetes mellitus characterized by insulin deficiency and insulin resistance due to other causes. The prevalence of type II diabetes mellitus is 90% or more of total patients with diabetes mellitus. Representative examples of complications accompanying diabetes include hyperlipidemia, hypertension, retinopathy and renal insufficiency (Paul Zimmer, et al., Nature, 2001, 414, 782). Sulfonylureas (stimulating insulin secretion in pancreatic cells), biguanides (inhibiting glucose production in the liver), α-glucosidase inhibitors (inhibiting glucose absorption in the intestines), etc. have been used as agents to treat diabetes. Recently, peroxisome proliferator-activated receptor gamma (PPARγ) accelerators (Thiazolidinediones, increasing insulin sensitivity) have drawn attention as therapeutic agents for diabetes. However, these drugs have side effects such as hypoglycemia, weight gain and the like (David E Moller, Nature, 2001, 414, 821). Accordingly, there is a strong need to develop diabetes therapeutic agents with decreased side effects, in particular without inducing hypoglycemia and weight gain.

Recently, it has been found that dipeptidyl peptidase-IV (DPP-IV) deficient mice rats maintained glucagon-like protein 1 (GLP-1) activity and high insulin levels, resulting in decreased blood glucose levels, which suggested the possibility of it being used as a therapeutic agent for diabetes (Marguet D. et al, Natl. Acad. Sci. USA, (2000) 97, 6874-6879). GLP-1 induces differentiation and growth of pancreatic β-cells in vivo and plays an important role in the production and secretion of insulin. GLP-1 is in-
activated by DPP-IV, and DPP-IV inhibitors have been reported to increase insulin secretion by means of inhibiting said inactivation mechanism. DPP-IV inhibitors are also being developed as a treatment for obesity because they lead to satiety in rats and slow down digestion of foods in the intestines, resulting in weight loss. Further, many investigators have also shown that DPP-IV inhibitors control blood glucose and lipid levels in animal experiments (Pospisilik J. A., et al, *Diabetes*, (2002) 51, 943-950). In this regard, DPP-IV inhibitors can be considered as potentially useful agents for treatment of diabetes.

**Disclosure of Invention**

**Technical Problem**

[4] To date, much research for developing DPP-IV inhibitors has focused on materials in which cyano group is bonded to pyrrolidine ring. For example, WO 00/34241 discloses DPP-IV inhibitors represented by the below formula.

![Formula 1](image1)

wherein R is an adamantyl group, and n is 0 to 3

[7] In addition, WO 01/96295 discloses DPP-IV inhibitors represented by the below formula.

![Formula 2](image2)

wherein Z is an alkyl group.

[10] These DPP-IV inhibitors are characterized by a cyano group introduced to a pyrrolidine ring. However, DPP-IV inhibitors having a carbonyl group introduced at the C-2 position of the pyrrolidine group of a heterocyclic ring, as disclosed in the present invention, have not been disclosed in the prior art.

**Technical Solution**

[11] The inventors of the present invention, while carrying out extensive research and many experiments to develop pyrrolidine-based compounds exhibiting DPP-IV
inhibitor effects, found that compounds having optionally substituted heteroarylcarbonyl group at the C-2 position of a pyrrolidine group have excellent inhibitory activity versus DPP-IV. The present invention was accomplished on the basis of such finding.

[12] It is therefore an object of the invention to provide pyrrolidine-based compounds of novel structure having good inhibitory activity versus DPP-IV.

[13] It is a further object of the present invention to provide processes for preparation of such novel pyrrolidine-based compounds.

[14] It is another object of the present invention to provide pharmaceutical compositions for inhibiting DPP-IV activity comprising a therapeutically effective amount of these pyrrolidine-based compounds as an active agent.

[15] It is another object of the present invention to provide methods for treating or preventing diseases caused by inappropriate activity of DPP-IV by the use of the pyrrolidine-based compounds of the present invention.

[16] Other objects and advantages of the present invention will become apparent to those skilled in the art from the following detailed description.

[17] According to the present invention, there are provided pyrrolidine-based compounds of Formula 1 below.

**Formula 1**

![Chemical Structure](image)

[21] wherein

[22] A is a substituent selected from the group consisting of:

[23] (i)

![Chemical Structure](image)

[24] (ii)
[25] (iii)

[26] wherein,

[27] R4 is each independently hydrogen; optionally substituted linear, branched, or cyclic saturated or unsaturated alkyl; optionally substituted aromatic or heteroaromatic ring; or optionally substituted heterocycle; and

[28] X is oxygen or sulfur;

[29] B is

\[
\begin{array}{c}
\text{R5} \\
\text{R6} \quad \text{N} \\
\end{array}
\]

, wherein

[30] R5 and R6 are each independently hydrogen; optionally substituted linear, branched, or cyclic saturated or unsaturated alkyl; optionally substituted aromatic or heteroaromatic ring; optionally substituted heterocycle; or R5 and R6 together are linked to form optionally substituted cycle or heterocycle;

[32] n is 0, 1 or 2;

[33] R3 is hydrogen, or C_{1-4} alkyl;

[34] Y is carbon, oxygen or sulfur;

[35] provided that where Y is carbon, R1 and R2 are each independently hydrogen or halogen, and where Y is oxygen or sulfur, R1 and R2 are not present.

**Best Mode for Carrying Out the Invention**

[36] The pyrrolidine-based compound(s) of Formula 1 as an active agent for treatment of diseases, even when a separate explanation is not added thereto, is intended to include a pharmaceutically acceptable non-toxic salt, hydrate, solvate, isomer, or prodrug thereof.

[37] As used herein, the term “pharmaceutically acceptable non-toxic salt” means alkali metal salts, alkaline earth metal salts, salts of inorganic acids, salts of organic acids, salts with amino acids, etc. The concrete examples of the pharmaceutical salts include
salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid; and salts of organic carboxylic acids such as acetic acid, trifluoroacetic acid, citric acid, formic acid, maleic acid, oxalic acid, succinic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, ascorbic acid or malic acid; or methanesulfonic acid or p-toluenesulfonic acid, and the like. These acid addition salts can be prepared by known methods on the basis of the said Formula 1. The compound of Formula 1 can also be treated with a base to form non-toxic salts, in which the base includes, for example, inorganic bases such as alkali metal hydroxides (for example, sodium hydroxide, potassium hydroxide), alkali metal hydrogencarbonates (for example, sodium bicarbonate, potassium bicarbonate), alkali metal carbonates (for example, sodium carbonate, potassium carbonate, calcium carbonate), etc. and amino acids.

[38] As used herein, the term "ester" means a compound species of formula -(R) -COOR where R and R' are each independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded via carbon of ring) and heteroalicyclic (bonded via a ring carbon), and n is 0 or 1.

[39] As used herein, the term "hydrate" means a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound thereto by non-covalent intermolecular forces.

[40] As used herein, the term "solvate" means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound thereto by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans.

[41] As used herein, the term "isomer" means a compound of the present invention or a salt thereof, that has the same chemical formula or molecular formula but is optically or stereochemically different therefrom. For example, since the carbon at C-2 position of proline ring (where heteroaryl ketone is substituted) becomes a chiral center, the compounds of Formula 1 may be present in the form of optical isomers such as enantiomers and partial stereoisomers.

[42] As used herein, the term "prodrug" means an agent that is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example of a prodrug, without limitation, would be a compound of the present invention which is ad-
ministered as an ester (the "prodrug") to facilitate transport across a cell membrane, but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell. A further example of a prodrug might be a short peptide (polyamino acid) bonded to an active group, where the peptide is metabolized to release the active moiety.

Other terms used herein can be interpreted as having their usual meanings in the art to which the present invention pertains. Some terms used in the present disclosure are briefly explained below.

When the term "optionally substituted" is used without any separate or additional descriptions in the present disclosure, it means that a substituent group(s) may be covalently bonded to the primary molecule or not. Herein, the substituent group(s) is(are) one or more group(s) individually and independently selected from alkyl, cycloalkyl (including dicycloalky and tricycloalkyl), perhaloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alloxy, alloxylalloxy, arylalkyloxy, aryloxy, mercapto, alkylthio, arylthio, cyan, halogen, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, Othiocarbamyl, Nthiocarbamyl, Camido, Namido, S-sulfonamido, Nsulfonamido, Ccarboxy, Ocarboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, pyrrolidinone, pyrrolidine, piperidine, piperazine, morpholine, amine, and amino, including mono and disubstituted amino groups, and the protected derivatives thereof. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, neopentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. However, the substituent group(s) is(are) not limited thereto but is(are) intended to include a variety of substituents. In any case, the substituent group(s) could also be optionally substituted. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neo-pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, and they could also be substituted individually and independently with the above exemplary groups.

As used herein, the term "aromatic" means an aromatic group which has at least one ring having a conjugated pi electron system and includes both carbocyclic aryl (e.g., phenyl) and heterocyclic aryl groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups.

The term "heteroaromatic" means an aromatic group which contains at least one
heterocyclic ring.

[47] The term "heterocycle" means a cyclic group in which one or more ring carbons are replaced with oxygen, nitrogen or sulfur and which includes, for example, but is not limited to furan, thiophene, pyrrole, pyrrole, pyrrolidone, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, triazole, thiadiazole, pyran, pyridine, piperidine, morpholine, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, etc.

[48] The term "alkyl" means an aliphatic hydrocarbon group. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[49] The alkyl group may have 1 to 20 carbon atoms. The alkyl group may also be a medium-sized alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds of the invention may be designated as "C$_1^1$-C$_4^4$ alkyl" or similar designations. By way of example only, "C$_1^1$-C$_4^4$ alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. These alkyl groups are optionally substituted with one or more of the above substituents.

[50] The substituent "R", as a designation used in the present disclosure, appearing by itself and without a number designation refers to a substituent selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl (bonded through a ring carbon), and optionally substituted heteroalicyclic (bonded through a ring carbon).

[51] An "O-carboxy" group refers to a RC(=O)O- group wherein R is as defined herein.

[52] A "C-carboxy" group refers to a -C(=O)OR group wherein R is as defined herein.

[53] An "acetyl" group refers to a -C(=O)CH$_3$ group.

[54] A "trihalomethanesulfonyl" group refers to a Z CS(=O)$_3^3$ group wherein Z is a halogen.

[55] A "cyano" group refers to a -CN group.

[56] An "isocyano" group refers to a -NCO group.
A "thiocyanato" group refers to a -CNS group.

An "isothiocyanato" group refers to a -NCS group.

A "sulfinyl" group refers to a -S(=O)-R group wherein R is as defined herein.

A "S-sulfonamido" group refers to a -S(=O)\(_2\)NR group wherein R is as defined herein.

A "N-sulfonamido" group refers to a RS(=O)\(_2\)NH- group wherein R is as defined herein.

A "trihalomethanesulfonamido" group refers to a Z\(\text{CS}(=O)\)\(_2\)NR- group wherein Z and R are as defined herein, respectively.

An "O-carbamyl" group refers to a -OC(=O)-NR group wherein R is as defined herein.

An "N-carbamyl" group refers to a ROC(=O)NH- group wherein R is as defined herein.

An "O-thiocarbamyl" group refers to a -OC(=S)-NR group wherein R is as defined herein.

An "N-thiocarbamyl" group refers to an ROC(=S)NH- group wherein R is as defined herein.

A "C-amido" group refers to a -C(=O)-NR\(_2\) group wherein R is as defined herein.

An "N-amido" group refers to a RC(=O)NH- group wherein R is as defined herein.

The term "perhaloalkyl" refers to an alkyl group in which all of the hydrogen atoms are replaced by halogen atoms.

Other terms used herein can be interpreted as having their usual meanings in the art to which the present invention pertains.

Preferably, A in Formula 1 above is a substituent of the below formula:

```
\begin{tikzpicture}
  \node (A) at (0,0) {X};
  \node (B) at (1,0) {N};
  \node (C) at (2,0) {N};
  \node (D) at (3,0) {R4};
  \draw (A) -- (B); \draw (B) -- (C); \draw (C) -- (D);
\end{tikzpicture}
```

wherein X is O, and R4 is hydrogen or \(\text{C}_1\) -\(\text{C}_4\) alkyl group.

Preferably, B in Formula 1 above is selected from the group comprising of the below substituents:

(i)
wherein R7 and R8 are each independently hydrogen, hydroxyl or amine group,

(ii)

wherein

R9 is hydrogen or C$_1$-$C_4$ alkyl group;

R10 and R11 are each independently hydrogen or optionally substituted lower alkyl, or R10 and R11 together are linked to form optionally substituted cycle or heterocycle group;

R12 is optionally substituted lower alkyl, optionally substituted cycloalkyl; optionally substituted aromatic or heteroaromatic ring; or optionally substituted heterocycle; and

n is 0 or 1,

(iii)

wherein R13 and R14 are each independently hydrogen, C$_1$-$C_4$ alkyl, hydroxyl, optionally substituted amine, or carboxyl group, the substitution taking place at two positions among C2 to C6 positions,

(iv)

wherein R15 and R16 are each independently hydrogen, C$_1$-$C_4$ alkyl, hydroxyl, optionally substituted amine, or carboxyl group, and n is 0 or 1, and

(v)
wherein R17 is hydrogen or C\textsubscript{1-4} alkyl group, and n is 0 or 1.

More preferably, B in Formula 1 is a substituent of the below formula:

wherein

R9, R10 and R11 are each independently hydrogen or methyl;

R12 is optionally substituted lower alkyl, optionally substituted cycloalkyl; optionally substituted aromatic or heteroaromatic ring; or optionally substituted heterocycle; and

n is 0 or 1.

In a preferred embodiment,

R9, R10 and R11 are each independently hydrogen or methyl;

R12 is amine, hydroxy, alkoxy, or C\textsubscript{1-4} alkyl group substituted with amine, hydroxy, alkoxy, or phenyl which is further substituted with hydroxy or halogen; and

n is 0 or 1.

Preferably, Y in Formula 1 above is carbene, and R1 and R2 are each independently hydrogen or fluorine atom.

In a preferable embodiment, the pyrrolidine-based compounds of Formula 1 is an optical isomer as represented in Formula 1a in which the carbon at C-2 position of proline ring is a chiral center:

\textbf{Formula 1a}
wherein A, B, R1, R2, R3 and Y are the same as in Formula 1.

The pyrrolidine-based compounds of Formula 1 above according to the present invention, as described in detail in the following experimental examples, have been shown to exhibit excellent inhibitory effects of DPP-IV activity. As explained in the above, DPP-IV inactivates glucagon-like peptide-1 (GLP-1). Since GLP-1 is a major stimulant of pancreatic insulin secretion, if the activity of DPP-IV enzyme is inhibited, insulin secretion would be accelerated, which in turn has an effect of lowering blood glucose. Accordingly, the pyrrolidine-based compounds of Formula 1 according to the present invention can be used in order to achieve the desired therapeutic or prophylactic effect of diabetes mellitus caused by DPP-IV (especially, type II diabetes), obesity and the like by means of inhibiting the activity of DPP-IV enzyme.

In a particularly preferred embodiment, the compounds of Formula 1 above are compounds as defined below:

2-(adamantane-1-ylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(adamantane-1-ylamino)-1-[2-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(adamantane-1-ylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(cyclopentyl-methyl-amino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(cyclohexyl-methyl-amino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(3-hydroxy-adamantane-1-ylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-tert-butylamino-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-piperidine-1-yl-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(octahydroquinoline-1-yl)-ethanone

2-(2-amino-1,1-dimethyl-ethylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
[122] 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2,6-dimethyl-piperidine-1-yl)-ethanone
[123] 2-tert-butylamino-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]ethanone
[124] 2-[2-(4-fluro-phenyl)-1,1-dimethyl-ethylamino]-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
[125] 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
[126] 2-(2-amino-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
[127] 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-[2-(4-fluro-phenyl)-1,1-dimethyl-ethylamino]-ethanone
[128] 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-[2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino]-ethanone
[129] 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-(2-cyclohexyl-2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
[130] 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamino)-ethanone
[131] N-2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethy lamino]-2-methyl-propyl-methanesulfonamide
[132] 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone
[133] 2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethyl amino]-2-methyl-propionic acid tert-butyl ester
[134] 2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethyl amino]-2-methyl-propionic acid
[135] 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
[136] 2-tert-butylamino-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
[137] 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
[138] 2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
[139] 2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-1-[2-(5-phenyl-[1,3,4]oxadiazole-
2-carbonyl)pyrrolidine-1-y1)-ethanone

2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-ethanone

2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

2-tert-butylamino-1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-ethanone

1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

2-(2-benzyloxy-1,1-dimethyl-ethylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-ethanone

2-(2-benzyloxy-1,1-dimethyl-ethylamino)-1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-ethanone

2-tert-butylamino-1-[2-(5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-y1]-ethanone

2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-ethanone

2-(1-hydroxymethyl-cyclopentylamino)-1-[2-(5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-ethanone

2-tert-butylamino-1-[2-(5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-y1]-ethanone

1-[2-(5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

1-[2-(5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-y1]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

2-tert-butylamino-1-[2-(5-(1-methyl-cyclopropyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-y1]-ethanone
[157] 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(1-methyl-cyclopropyl)-1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[158] 2-(1-hydroxymethyl-cyclopentylamino)-1-[2-[5-(1-methyl-cyclopropyl)-1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[159] 2-tert-buty lamino-1-[2-[5-(2,4,6-trimethyl-phenyl)-1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[160] 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2,4,6-trimethyl-phenyl)-1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[161] 2-(1-hydroxymethyl-cyclopentylamino)-1-[2-[5-(2,4,6-trimethyl-phenyl)-1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[162] 1-[2-[5-tert-buty]-[1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-2-[(2-hydroxy-ethyl)-methyl-amino]-ethanone

[163] 3-tert-buty lamino-1-[2-[5-tert-buty]-[1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-propane-1-one

[164] 1-[2-[5-tert-buty]-[1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-3-[(2-hydroxy-ethyl)-methyl-amino]-propane-1-one

[165] 1-[2-[5-tert-buty]-[1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-3-[(2-hydroxymethyl)-piperidine-1-yl]-propane-1-one

[166] 6-(2-[2-[5-tert-buty]-[1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide

[167] 6-(2-[3-[2-(5-tert-buty)-[1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-3-oxo-propylamino)-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide

[168] 1-[2-(5-tert-buty)-[1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-3-(3-trifluoromet hyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-propane-1-one

[169] 1-[1-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazone-2-carbonyl]-pyrrolidine-1-yl]-2-[1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamino]-ethanone

[170] 2-tert-buty lamino-1-[(2S)-(5-tert-buty)-[1,3,4]oxadiazone-2-carbonyl]-2-methyl-pyrrolidine-1-yl]-ethanone

[171] 1-[(2S)-(5-tert-buty)-[1,3,4]oxadiazone-2-carbonyl]-2-methyl-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[172] 2-(adamantane-1-ylamino)-1-[4S-fluoro-2-(5-methyl-[1,3,4]oxadiazone-2-carbonyl)]-2-methyl-pyrrolidine-1-yl]-ethanone

[173] 1-[4S-fluoro-2-(5-methyl-[1,3,4]oxadiazone-2-carbonyl)]-2-pyrrolidine-1-yl]-2-(1-m ethyl-1-phenyl-ethylamino)-ethanone

[174] 2-tert-buty lamino-1-[2-(5-tert-buty)-[1,3,4]oxadiazone-2-carbonyl]-4S-fluoro-pyrrol
idine-1-yl]-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone

2-tert-butylamino-1-[4S-fluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

1-[4S-fluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cycloproplamino)-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone

2-[2-(2-2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-oxoethylamino]-2-methyl-propionic acid tert-butyl ester

2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-oxoethylamino]-2-methyl-propionic acid

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-(2-methoxyethoxy-1,1-dimethyl-ethylamino)-ethanone

2-tert-butylamino-1-[4S-fluoro-2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

1-[4S-fluoro-2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

1-[4S-fluoro-2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

1-[4S-fluoro-2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxyethoxy-1,1-dimethyl-ethylamino)-ethanone

2-tert-butylamino-1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-ethanone
[192] 1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-y1]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[193] 1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-y1]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

[194] 1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-y1]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

[195] 2-tert-butylamino-1-[4S-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-y1]-ethanone

[196] 1-[4S-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-y1]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[197] 2-tert-butylamino-1-[2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-y1]-ethanone

[198] 1-[2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-y1]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[199] 1-[2-[5-(1,1-dimethyl-propyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-y1]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[200] 2-tert-butyl-1-[4S-fluoro-2-[5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-y1]-ethanone

[201] 1-[4S-fluoro-2-[5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-y1]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[202] 1-[4S-fluoro-2-[5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-y1]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[203] 2-tert-butyl-1-[4S-fluoro-2-[5-(2,4,6-trimethyl-phenyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-y1]-ethanone

[204] 1-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-y1]-2-[(2-hydroxy-ethyl)-methyl-amino]-ethanone

[205] 1-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-y1]-3-[(2-hydroxy-1,1-dimethyl-ethylamino)-propane-1-one

[206] 1-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-y1]-3-[(2-hydroxy-ethyl)-methyl-amino]-propane-1-one

[207] 1-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-y1]-3-[(2-hydroxymethyl-piperidine-1-y1)-propane-1-one

[208] 6-(2-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-y1]-2-oxo-ethylamino)-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide

[209] 6-(2-[3-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-y1]-
3-oxo-ethylamino)-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide

1-[2-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-[1,1-dimethyl-2-(pyridine-2-ylamino)-ethanol

1-[2-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-ethane

1-[2-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(1-benzyl-4-methyl-piperidine-4-ylamino)-ethanol

1-[2-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(4-methyl-1-piperidine-4-yl-piperidine-4-ylamino)-ethanol

1-(4-[2-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino]-4-methyl-piperidine-1-yl)-2-hydroxy-ethanol

2-(adamantane-1-ylamino)-1-[4,4-difluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanol

2-(adamantane-1-ylamino)-1-[4R-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-thiazoline-3-yl]-ethanol

2-(3-hydroxy-adamantane-1-ylamino)-1-[4R-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanol

1-[4R-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-2-[2-(4-fluorophenyl)-1,1-dimethyl-ethylamino]-ethanol

1-[4-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-2-[2-methoxy-1,1-dimethyl-ethylamino]-ethanol

1-[4-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanol

2-tert-butylamino-1-[2-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanol

2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanol

2-tert-butylamino-1-[2-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanol

2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[4S-fluoro-2-(5-tert-buty1-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanol

2-(adamantane-1-ylamino)-1-[2-(3-methyl-[1,2,4]oxadiazole-5-carbonyl)-pyrrolidine-1-yl]-ethanol

2-(3-hydroxy-adamantane-1-ylamino)-1-[2-(3-methyl-[1,2,4]oxadiazole-5-carbonyl)-pyrrolidine-1-yl]-ethanol
2-(adamantane-1-ylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidin-1-yl]-ethanone
2-tert-butylamino-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-[(1-benzyl-2-hydroxy-1-methyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-[2-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-[2-(4-fluorophenyl)-1,1-dimethyl-ethylamino]-ethanone
2-tert-butyl-1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-tert-butyl-1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-ethyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxymethylcyclopropylamine)-ethanone
2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone
2-methyl-2-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(oxo-ethylamino)-ethanone
hylamino)-propionic acid tert-butyl ester

[245] 2-tert-butylamino-1-(2-((5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)-ethanone

[246] 1-[2-((5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[247] 2-methyl-2-[2-((5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-2-(oxo-ethylamino)-propionic acid trifluoroacetate

[248] 1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone

[249] 2-(1-hydroxymethyl-cyclopentylamino)-1-[2-((5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-ethanone

[250] 1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[251] 1-[-2-((5-(methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[252] 2-tert-butylamino-1-[2-[(5-(methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-ethanone

[253] 1-[-2-((5-(methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[254] 1-[-2-[(5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[255] 2-tert-butyl-1-[2-[(5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-ethanone

[256] 1-[-2-[(5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[257] 2-(methoxymethoxy-1,1-dimethyl-ethylamino)-1-[-2-((5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-ethanone

[258] 2-(methoxy-1,1-dimethyl-ethylamino)-1-[-2-((5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-ethanone

[259] 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[-2-((5-(methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-ethanone

[260] 2-tert-butylamino-1-[-2-((5-(methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-ethanone

[261] 2-(1-hydroxymethyl-cyclopentylamino)-1-[-2-((5-(methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)]-ethanone
[262] 1-[(2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl)-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

[263] 2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[(2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl)-ethanone

[264] 1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[265] 2-tert-butylamino-1-[(2-[5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl)-ethanone

[266] 1-[(2-[5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl)-2-(1-hydroxyethyl-cyclopentylamino)-ethanone

[267] 1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

[268] 1-[2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

[269] 1-[2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

[270] 1-[2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

[271] 2-tert-butylamino-1-[(2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl)-ethanone

[272] 1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

[273] 1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

[274] 2-(2-benzylxoy-1,1-dimethyl-ethylamino)-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[276] 2-(2-benzylxoy-1,1-dimethyl-ethylamino)-1-[2-[5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[277] 2-(2-benzylxoy-1,1-dimethyl-ethylamino)-1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

[278] 1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

[279] 1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1
-dimethyl-ethylamino)-ethane

[280] 2-(2-benzoyloxy-1,1-dimethyl-ethylamino)-1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

[281] 2-tert-butyl-1-[2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethane

[282] 1-[2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[283] 2-(1-hydroxymethyl-cyclopentylamino)-1-[2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[284] 2-tert-butylamino-1-[2-[5-(2-methoxy-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[285] 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2-methoxy-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[286] 2-(1-hydroxymethyl-cyclopentylamino)-1-[2-[5-(2-methoxy-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[287] 2-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino]-1-[2-[5-(2-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[288] 2-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino]-1-[2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[289] 1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino]-ethanone

[290] 1-[2-[5-adamantane-1-yl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-tert-butylamino-ethanone

[291] 1-[2-[5-adamantane-1-yl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[292] 1-[2-[5-adamantane-1-yl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[293] 2-tert-butylamino-1-[2-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[294] 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[295] 2-(1-hydroxymethyl-cyclopentylamino)-1-[2-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[296] N-(2-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propyl-acetamide
[297] N-[2-(acetyl-[2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-oxo-ethyl]-amino)-2-methyl-propyl]-acetamide

[298] 6-(2-methyl-2-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-oxo-ethylamino)-propylamino)-pyridine-3-sulfonic acid dimethyl amide

[299] 2-tert-butylamino-1-[(4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[300] 1-[(4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[301] 2-tert-butylamino-1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-ethanone

[302] 1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[303] 1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone

[304] 2-tert-butylamino-1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-ethanone

[305] 1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[306] 1-[(4S)-2-[(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[307] 1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[308] 2-tert-butyl-1-[(4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[309] 1-[(4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[310] 1-[(4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[311] 1-[(4S)-4-fluoro-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone

[312] 2-(2-cyclohexyl-2-hydroxy-1,1-dimethyl-ethylamino)-1-[(4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[313] 1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-2-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamine)-ethanone

[314] 1-[(4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-2-pyrrolidine-1-yl]-2-(
1-hydroxymethyl-cyclopropylamine)-ethanone

[315] 1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

[316] 1-[(4S)-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

[317] 1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-ethanone

[318] 1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(3-trifluoroethyl-5,6-dihydro-8H-[1,2,4]triazol[4,3-a]pyrazine-7-yl)-ethanone

[319] 6-[(2-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propylamino]-pyridine-3-sulfonic acid dimethylamidate

[320] 1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(4-methyl-1-pyrimidine-2-yl-piperidine-4-ylamino)-ethanone

[321] 1-[(2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-[1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamino]-ethanone

[322] 1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-[1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamino]-ethanone

[323] Among the above compounds, 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[4S-fluoro-2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone is particularly preferable.

[324] The present invention also relates to processes for preparation of the pyrrolidine-based compounds of Formula 1. A person skilled in the art to which the present invention pertains could easily manufacture the pyrrolidine-based compounds of Formula 1 on the basis of the chemical structure by various processes. Therefore, it is to be understood that said processes fall within the scope of the present invention.

[325] As an illustrative process for such preparation, the compound of Formula 1 can be prepared by reacting a compound of Formula 2 below:

[328] **Formula 2**

[329]
[330] wherein A, R1, R2, R3 and Y are the same as defined in Formula 1; and W is a reactive group such as halogen element,

[331] with an amine compound (BH) which corresponds to substituent B in the compound of Formula 1.

[332] As used herein, the term "amine compound (BH) which corresponds to substituent B" means an amine compound having a hydrogen atom in the substituent A defined in Formula 1 at the reaction site with a compound of Formula 2.

[333] As a detailed explanation of the above-mentioned reaction, a compound of Formula 2 can be reacted with 1 to 3 equivalents of an amine compound (BH) on the basis of the compound of Formula 2 in the presence of an organic solvent such as dichloromethane, cyclic ether (e.g., tetrahydrofuran) and the like at a temperature of 0 to 40°C. In the reaction, the product is present in a form of a diastereomeric mixture, being a mixture of epimers, because the carbon at C-2 position of proline ring (where heteroaryl ketone is substituted) becomes chiral center as mentioned above.

[334] The reaction product can be isolated and purified from the reactants by means of conventional methods such as recrystallization, ion electrophoresis, silica gel column chromatography, ion exchange resin chromatography and the like. These isolation and purification methods can also be used in the preparation processes described below.

[335] The compound of Formula 2 can also be prepared by a person skilled in the art on the basis of its chemical structure by various methods. In an illustrative embodiment, the compound of Formula 2 can be prepared from the compound of Formula 3, as shown in Reaction Scheme 1 below:

[336] **Reaction Scheme 1**

[337] ![Diagram](attachment:image.png)
wherein

A, R1, R2, R3, W and Y are the same as defined in Formula 2;

PG is Boc, Cbz or Fmoc wherein Boc means t-butoxycarbonyl, Cbz means benzylloxycarbonyl, and Fmoc means 9-fluorenlymethoxycarbonyl;

"a" is TFA or HCl where PG is Boc; H/Pd/C or TMSI where PG is Cbz; and Et2NH where PG is Fmoc; and

"b" is WCH2COW, wherein W is the same as defined above.

The amine group having a ring structure in the compound of Formula 3 is protected by PG1, which is removed through the step (a) and then reacted with about 1 equivalent or more of WCH2COW (haloacetyl halide) and bases to form a compound of Formula 2. The typical examples of the haloacetyl halide include bromoacetyl bromide, chloroacetyl chloride and the like, and the typical examples of the bases include potassium carbonate, triethylamine and the like. The reaction can be preferably conducted in the presence of inactive organic solvents (e.g., tetrahydrofuran), chlorinated hydrocarbons (e.g., dichloromethane) at a temperature of 0 to 50°C.

The reactants used in the preparation processes according to the present invention are known compounds, or can be easily synthesized by a person skilled in the art, even if they were not known.

For example, the pentagonal heterocyclic ring moiety in A of the compound of Formula 3 can be synthesized by various known methods (for example J. Med. Chem., 1991, 34, 2060-2067). As a representative example, a compound containing 1,3,4-oxadiazole ring (compound of Formula 3 below) can be synthesized with reference to known publications (for example J. Med. Chem. 2001, 44, 1268-1285) in accordance with Reaction Scheme 2 or 3 below:

**Reaction Scheme 2**

![Reaction Scheme 2](image)

**Reaction Scheme 3**

![Reaction Scheme 3](image)
[350] wherein 
[351] PG, R1, R2, R3, R4, X and Y are the same as defined in Reaction Scheme 1; 
[352] "a" is HNMe(OMe)/EDC/HOBt, wherein Me means methyl group, EDC means 1-[3-(dimethylamino)propyl]-3-ethylcarbo-di-imide hydrochloride and HOBT means 1-hydroxybenzotriazol hydroxide; 
[353] "b" is 1,3,4-oxadiazole/nBuLi, wherein Bu means butyl group; 
[354] "c" is CICO Et/Et N; NaN3 - [O]; 
[355] "d" is oxadiazole/nBuLi, wherein Bu means butyl group; and 
[356] "e" is Dess-Martin[O]. 
[357] The first reaction in Reaction Scheme 2 can, for example, be conducted by reacting a carboxylic acid compound of Formula 4 with methoxymethylaniline (HNMe(OMe)), EDC and HOBT in the presence of dimethylformamide solvent at a temperature of 15 to 30°C. 
[358] The second reaction in Reaction Scheme 2 can, for example, be conducted by adding dropwise n-butyllithium (nBuLi) in a cyclic ether (for example THF) solvent to 1,3,4-oxadiazole and then adding Weinreb amide (a compound of Formula 5) to the resulting solution. The reaction temperature is raised gradually from -78 to 25°C, as the reaction proceeds. 
[359] The first reaction in Reaction Scheme 3 can, for example, be conducted by reacting a carboxylic acid of Formula 6, commercially available, with primary alcohol in the presence of cyclic ether (for example THF) solvent through reduction and oxidation to obtain a compound of Formula 7.
[360] The second reaction in Reaction Scheme 3 can be conducted by adding dropwise n-butyllithium (nBuLi) to 1,3,4-oxadiazole and then adding dropwise an aldehyde (a compound of Formula 7) to the resulting solution to obtain a compound of Formula 8. The reaction temperature is raised gradually from -78 to 25°C, as the reaction proceeds.

[361] The third reaction in Reaction Scheme 3 can be conducted by reacting a compound of Formula 8 with Dess-Martin periodinane in the presence of dichloromethane solvent to give a ketone compound (a compound of Formula 3).

[362] A compound of Formula 3" can be synthesized directly from a compound of Formula 4' through Reaction Scheme 4 below:

**Reaction Scheme 4**

(4')

Wherein

(3')

[365] PG₁, R₁, R₂, R₃, R₄ and Y are the same as defined in reaction scheme 1;

[366] X is oxygen atom; and

[368] "e" is 1,3,4-oxadiazole/nBuLi wherein Bu means butyl group.

[369] The reaction in Reaction Scheme 4 can, for example, be conducted by adding dropwise n-butyllithium in cyclic ether (for example THF) solvent to 1,3,4-oxadiazole and then adding a compound of Formula 4' to the resulting solution. The reaction temperature is raised gradually from -78 to -35 to -30°C, as the reaction proceeds, and stirred at that temperature for about 2 to 3 hours.

[370] In another embodiment, a compound of Formula 3" wherein A in a compound of Formula 1 is a substituent (ii) can be obtained through reaction scheme 5 below:

**Reaction Scheme 5**

[372]
wherein
[373]  PG₁, R₁, R₂, R₃, R₄ and Y are the same as in Formula 1 and Reaction Scheme 1;
[374]  PG₂ is allylalkyl or tert-butyltrimethylsilane;
[375]  "a" is NaHSO₃/NaCN;
[376]  "b" is ethylvinylether/ppTs, DHP/ppTs or TBSCl/imidazole, wherein ppTs means p-toluenesulfonyl acid pyridinate, DHP means dihydropyran and TBSCl is tert-butyltrimethylsilyl;
[377]  "c" is H₂NOH;
[378]  "d" is CDI/R₃CO₂H wherein CDI is 1,1-carbodiimide and R₃ is the same as in the above;
[379]  "e" is ppTs; and
[380]  "f" is Dess-Martin periodinane.
[381]  In Reaction Scheme 5, a compound of Formula 14 can be directly synthesized from a compound of Formula 12 through Reaction Scheme 6 below:
[382]  Reaction Scheme 6
wherein
"e" is R4CO Cl/pyridine.

The reaction can be conducted at a temperature of 100 to 130°C.

The more detailed explanation of the above reaction schemes 4 and 5 is as follows.

A compound of Formula 9 is reacted with NaHSO3 and NaCN in the presence of water solvent at a temperature of 0°C to give a compound of Formula 10. The compound of Formula 10 is reacted with ethylvinylether and ppTs in the presence of dichloromethane solvent at room temperature to give a compound of Formula 11. Separately a hydroxylamine hydrochloride is reacted with a base in the presence of alcohol solvent at room temperature, which is reacted with the compound of Formula 11 under reflux to give a compound of Formula 12. A carboxylic acid compound (R3COO2 H) is activated by the reaction with 1,1-carbodiimide (CDI) in the presence of DMF solvent at room temperature. To this is added the compound of Formula 12 and the mixture is then allowed to warm to 40 ~ 110°C, resulting in a compound of Formula 13. After removing the alcohol-protecting group in the compound of Formula 13, the resulting alcohol is oxidized to give a compound of Formula 3". The compound of Formula 14 can be directly synthesized from the compound of Formula 12 (refer to Reaction Scheme 5 above).

In another embodiment, a compound of Formula 3" wherein A in the compound of Formula 1 is substituent (iii) can be synthesized through reaction scheme 7 below:

**Reaction Scheme 7**
wherein
PG₁, R₁, R₂, R₃, R₄ and Y are the same as in Formula 1 and Reaction Scheme 1;
"a" is NaH₂SO₃/NaCN;
"b" is dioxane/6N HCl;
"c" is Boc₂O, NaOH;
"d" is CDI/R₃C(=NOH)NH₂, wherein CDI is 1,1-carbodiimide; and
"e" is Dess-Martin periodinane.

The more detailed explanation of the above reaction schemes 7 is as follows.

A compound of Formula 10 is obtained in the same manner described in Reaction Scheme 5. To the compound of Formula 10 is added dropwise dioxane and concentrated hydrochloric acid solvent in ratio of 1:1 and refluxed to give a hydrolyzed compound of Formula 15. Without any isolation and purification, the amine salt is converted to butyloxy carbonyl group at room temperature to give a compound of Formula 16. The compound of Formula 16 is activated through the reaction with 1,1-carbodiimide in the presence of DMF solvent at room temperature. To this are added various amidoxime compounds and warmed to 40–110°C to give a compound.
of Formula 17. The alcohol group in the compound of Formula 17 is oxidized to give a compound of Formula 3".

[402] As described above, the compounds according to the present invention, starting materials for preparation thereof and intermediates can be synthesized by various methods, which should be interpreted to be included within the scope of the present invention in connection with the preparation of the compound of Formula 1.

[403] Also, the present invention provides a pharmaceutical composition for inhibiting DPP-IV comprising (a) a therapeutically effective amount of pyrrolidine-based compound of Formula 1, and (b) a physiologically acceptable carrier, diluent, or excipient, or a combination thereof.

[404] The term "pharmaceutical composition" as used herein means a mixture of a compound of the invention with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to oral, injection, aerosol, parenteral, and topical administrations. Pharmaceutical compositions can also be obtained by reacting compounds with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[405] The term "therapeutically effective amount" means that amount of the compound being administered which will alleviate to some extent one or more of the symptoms of the disease being treated. Thus, a therapeutically effective amount refers to that amount which has the effect of (i) reversing the rate of progress of a disease; (ii) inhibiting to some extent or preferably, completely ceasing further progress of the disease; and/or, (iii) alleviating to some extent (or, preferably, eliminating) one or more symptoms associated with the disease.

[406] The term "carrier" means a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example, dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

[407] The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the ionic strength conditions of human blood. Since buffer salts can control the pH of a
solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

[408] The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

[409] The pyrrolidine-based compounds of Formula 1 can be administered in various pharmaceutical dosage forms in accordance with intended use. In the preparation of pharmaceutical compositions in accordance with the present invention, an active agent, more specifically a compound of Formula 1 may be mixed with one or more physiologically acceptable carriers which can be selected depending on the dosage form to be prepared. For example, the pharmaceutical composition according to the present invention can be formulated into dosage forms suitable for injection or oral administration.

[410] The compounds of Formula 1 may be formulated in a conventional manner using known physiologically acceptable carriers and excipients and presented in unit dosage form or in multidose containers. The formulations may take such forms as solutions, suspensions or emulsions in oily or aqueous vehicles, and may contain conventional dispersing, suspending or stabilizing agents. Alternatively, the active ingredient may be in powder form for reconstitution with sterile pyrogen-free water, before use. The compounds of Formula 1 may also be formulated into suppositories containing conventional suppository bases such as cocoa butter or other glycerides. Solid dosage forms for oral administration include capsule, tablet, pill, powder and granule. Preferable dosage forms are capsule and tablet. It is preferable that tablets and pills be coated. The solid dosage forms for oral administration may be obtained by mixing the compounds of Formula 1 as an active agent with inactive diluents such as sucrose, lactose, starch and the like and carriers such as lubricant, for example magnesium stearate, including disintegrator, binder and the like.

[411] If necessary, the compounds of Formula 1 and compositions comprising the same according to the present invention may be administrated in combination with other pharmaceutical agents, for example, other diabetes treating agents.

[412] The term "therapeutically effective amount" means an amount of active ingredients effective to alleviate, ameliorate or prevent symptoms of disease or decrease or delay the onset of clinical markers or symptoms of disease. The therapeutically effective amount may be determined by experiments on the efficacy of compounds as an active agent via in vivo and in vitro known model systems for diseases to be treated.

[413] When the formulation is presented in unit dosage form, the compounds of Formula
1 as an active agent can be preferably contained in an amount of about 0.1 ~ 1,500 mg unit dosage. The dosage amount of the compounds of Formula 1 will be dependent on the subject's weight and age, the nature and severity of the affliction and the judgment of the prescribing physician. For adult administration, the dosage amount required will be about in the range of 1 to 500 mg a day depending on the frequency and strength of the dosage. For intramuscular or intravenous administration to adults, a total dosage amount of about 5 ~ 300 mg a day will be sufficient. In some patients, the dosage amount in a day will be higher than that.

[414] The present invention provides processes for treating or preventing diseases involving inappropriate activity of DPP-IV by the use of effective amounts of the compounds of Formula 1. Representative examples of the diseases caused by inappropriate levels of DPP-IV include, but are in no way limited to, diabetes mellitus, obesity and the like as described above. Among diabetes mellitus, the present invention is preferred to treat and prevent type II diabetes mellitus. The term "treating" means ceasing or delaying progress of diseases when the compounds of Formula 1 or compositions comprising the same are administered to subjects exhibiting symptoms of diseases. The term "preventing" means ceasing or delaying symptoms of diseases when the compounds of Formula 1 or compositions comprising the same are administered to subjects exhibiting no symptoms of diseases, but having high risk of developing symptoms of diseases.

**Mode for the Invention**

[415] The present invention will now be illustrated in more detail by the following preparations and examples. However, it will be understood that the present invention is not limited to these specific preparations and examples, but is subject to various modifications that will be recognized by one skilled in the art to which the present invention pertains.

[416]

[417] **PREPARATION 1: Synthesis of 2S-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester**

[418] 2.15 g (10 mmol) of pyrrolidine-1,2S-dicarboxylic acid 1-tert-butyl ester and 0.975 g (10 mmol) of methoxyethylamine were dissolved in dimethylformamide. To the solution were added 2.49 g (13 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbo-di-imide hydrochloride (EDC) and 1.76 g (13 mmol) of 1-hydroxybenzotriazole hydrate (HOBT), followed by addition of 5.6 ml (40 mmol) of
triethylamine and stirring for 18 hours. The reaction was diluted with excess ethyl acetate, and the product was washed once with aqueous 1N HCl and aqueous NaCl, respectively, dried over anhydrous magnesium sulfate, and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 2) to give 1.8 g of the title compound in a yield of 70%.

[419] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.6-4.8 (1H, m), 37-3.8 (3H, m), 3.4-3.7 (2H, m), 3.22 3H, s), 2.1-2.3 (1H, m), 1.8-2.1 (3H, m), 1.4-1.5 (9H, m)

[420] Mass (m/e) 259 (M+1)

[421]

[422] PREPARATION 2: Synthesis of 2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

[423] 0.98 g (11.66 mmol) of 2-methyl-1,3,4-oxadiazole was dissolved in tetrahydrofuran and the temperature of the reactor was cooled to -78°C. To this was added dropwise 47 ml of butyl lithium (2.5M in hexane) and the resulting mixture was stirred for 40 minutes. To this was added 3.0 g (11.6 mmol) of magnesium bromide ethylether complex, followed by stirring for 40 minutes at the same temperature. 1.0 g (3.87 mmol) of 2-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester obtained in PREPARATION 1 was dissolved in tetrahydrofuran and then added to the solution previously formed. Thereafter, the temperature was gradually raised to room temperature. After stirring for about 3 hours, the reactants were diluted with ethyl acetate, washed once with aqueous saturated ammonium chloride and aqueous NaCl, respectively, dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate = 1 : 1) to give 0.526 g of the title compound in a yield of 50%.

[424] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.29 (1H, m), 3.5-3.7 (2H, m), 2.6-2.8 (3H, m), 2.4-2.5 (1H, m), 1.9-2.1 (3H, m), 13-1.5 (9H, m)

[425] Mass (m/e) 268 (M+1)

[426]


[428] The title compound was prepared in the same manner as in PREPARATION 2. Yield 473%

[429] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.2-5.3 (1H, m), 3.5-3.7 (2H, m), 2.9-3.1 (2H, m), 2.4-2.5 (1H,
m), 1.9-2.1 (3H, m), 13-1.5 (9H, m), 1.2-13 (3H, m)
[430] Mass (m/e) 296 (M+1)
[431]
[432] PREPARATION 4: Synthesis of 2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester
[433] The title compound was prepared in the same manner as in PREPARATION 2. Yield 18.4%
[434] ¹H NMR (CDCl₃) δ 5.2-5.3 (1H, m), 3.5-37 (2H, m), 2.4-2.5 (1H, m), 1.9-2.1 (3H, m), 13-1.5 (18H, m)
[435] Mass (m/e) 324 (M+1)
[436]
[437] PREPARATION 5: Synthesis of 2S-[5-(1,1-dimethyl-propyl)[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester
[438] The title compound was prepared in the same manner as in PREPARATION 2. Yield 40.8%
[439] ¹H NMR (CDCl₃) δ 5.2-5.3 (1H, m), 3.5-37 (2H, m), 2.4-2.5 (1H, m), 1.9-2.1 (3H, m), 1.43 (2H, q, J = 7.5 Hz), 1.40 (9H, s), 0.82 (3H, t, J = 7.5 Hz)
[440] Mass (m/e) 338 (M+1)
[441]
[443] The title compound was prepared in the same manner as in PREPARATION 2. Yield 76.7%
[444] ¹H NMR (CDCl₃) δ 80-82 (2H, m), 7.4-7.6 (3H, m), 53-5.4 (1H, m), 3.5-37 (2H, m), 2.4-2.6 (1H, m), 1.9-2.1 (3H, m), 13-1.5 (9H, s)
[445] Mass (m/e) 344 (M+1)
[446]
[447] PREPARATION 7: Synthesis of 2S-[5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester
[448] The title compound was prepared in the same manner as in PREPARATION 2. Yield 43.2%
[449] ¹H NMR (CDCl₃) δ 5.2-5.3 (1H, m), 3.5-37 (2H, m), 2.9-3.1 (1H, m), 2.4-2.5 (1H, m), 1.2-2.1 (13H, m)
[450] Mass (m/e) 350 (M+1)
[451]
PREPARATION 8: Synthesis of 2S-[5-(1-methyl-cyclohexyl)-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in PREPARATION 2. Yield 39.1%

$^1$H NMR ($\text{CDCl}_3$) $\delta$ 5.2-5.3 (1H, m), 3.5-3.7 (2H, m), 2.4-2.5 (1H, m), 2.1-2.3 (2H, m), 1.9-2.1 (3H, m), 1.2-1.8 (11H, m)

Mass (m/e) 364 (M+1)

PREPARATION 9: Synthesis of 2S-[5-(1-methyl-cyclopropyl)-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in PREPARATION 2. Yield 60.3%

$^1$H NMR ($\text{CDCl}_3$) $\delta$ 5.2-5.3 (1H, m), 3.5-3.7 (2H, m), 2.4-2.5 (1H, m), 1.9-2.1 (3H, m), 1.6 (3H, s), 1.45 (2H, m), 1.1 (2H, m),

Mass (m/e) 322 (M+1)

PREPARATION 10: Synthesis of 2S-[5-(2,4,6-trimethyl-phenyl)-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in PREPARATION 2. Yield 43.4%

$^1$H NMR ($\text{CDCl}_3$) $\delta$ 6.98 (2H, s), 5.2-5.3 (1H, m), 3.5-3.7 (2H, m), 2.4-2.5 (1H, m), 1.9-2.1 (3H, m), 232 (3H, s), 2.28 (6H, s)

Mass (m/e) 386 (M+1)

PREPARATION 11: Synthesis of 2-bromo-1-[2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

0.526 g (1.97 mmol) of 2-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 2 was dissolved in 34M HCl/EA, and the solution was stirred for about 20 minutes and then distilled off under reduced pressure. The resulting compound, (5-methyl-[1,3,4]oxadiazole-2-yl)-pyrrolidine-2S-yl-methanone), was dissolved in about 15 ml of dichloromethane and then cooled to 0°C. To this were added dropwise in sequence 0.18 ml (20 mmol) of bromoacetyl bromide and 0.5 ml (36 mmol) of triethylamine, followed by stirring for about 40 minutes. Water was added to quench the reaction, which was extracted 3 times with dichloromethane. The
extracted organic layer was separated, washed once with aqueous NaCl, dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 2) to give 0.11 g of the title compound in a yield of 20% (two steps).

\[ 1H \text{ NMR (CDCl}_3 \text{) } \delta \ 5.4 \ (1H, \text{ m}), \ 3.8 \ (2H, \text{ ABq, } J=16\text{Hz}), \ 37-39 \ (2H, \text{ m}), \ 27 \ (3H, \text{ s}), \ 2.5 \ (1H, \text{ m}), \ 2.0-23 \ (3H, \text{ m}) \]

Mass (m/e) 302, 304 (M, M+2)

[470]

PREPARATION 12: Synthesis of 2-bromo-1-[2S-(5-ethyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

The title compound was prepared in the same manner as in PREPARATION 11.
Yield : 55%

\[ 1H \text{ NMR (CDCl}_3 \text{) } \delta \ 5.4-5.5 \ (1H, \text{ m}), \ 3.9 \ (2H, \text{ ABq, } J=11\text{Hz}), \ 37-39 \ (2H, \text{ m}), \ 30 \ (2Hq, \text{ J = 7.5 Hz}), \ 24-2.5 \ (1H, \text{ m}), \ 20-2.2 \ (3H, \text{ m}), \ 1.44 \ (3H, \text{ t, J = 7.5 Hz}) \]

Mass (m/e) 317, 319 (M, M+2)

[475]

PREPARATION 13: Synthesis of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

The title compound was prepared in the same manner as in PREPARATION 11.
Yield : 30.6%

\[ 1H \text{ NMR (CDCl}_3 \text{) } \delta \ 5.4-5.5 \ (1H, \text{ m}), \ 3.85 \ (2H, \text{ ABq, } J=11\text{Hz}), \ 37-39 \ (2H, \text{ m}), \ 24-2.5 \ (1H, \text{ m}), \ 2.1-2.2 \ (3H, \text{ m}),1.5 \ (9H, \text{ s}) \]

Mass (m/e) 344, 346 (M, M+2)

[480]

PREPARATION 14: Synthesis of 2-bromo-1-[2S-(5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

The title compound was prepared in the same manner as in PREPARATION 11.
Yield : 85%

\[ 1H \text{ NMR (CDCl}_3 \text{) } \delta \ 5.4-5.5 \ (1H, \text{ m}), \ 3.85 \ (2H, \text{ ABq, } J=15\text{Hz}), \ 37-39 \ (2H, \text{ m}), \ 2.4-2.5 \ (1H, \text{ m}), \ 2.1-2.2 \ (3H, \text{ m}), \ 1.8 \ (2H, \text{ q, J = 7.5 Hz}), \ 1.42 \ (9H, \text{ s}), \ 0.84 \ (3H, \text{ t, J = 7.5 Hz}) \]

Mass (m/e) 358, 360 (M, M+2)

[485]

PREPARATION 15: Synthesis of 2-bromo-1-[2S-(5-phenyl-[1,3,4]
oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

[488] The title compound was prepared in the same manner as in PREPARATION 11. Yield: 85%

[489] $^1$H NMR (CDCl$_3$) $\delta$ 8.15 (2H, d, $J = 7.5$ Hz), 7.6 (1H, t, $J = 7.5$ Hz), 7.54 (2H, t, $J = 7.5$ Hz), 5.4-5.5 (1H, m), 3.84 (2H, Abq, $J = 10$Hz), 3.37-3.9 (2H, m), 2.4-2.5 (1H, m), 2.1-2.2 (3H, m)

[490] Mass (m/e) 364, 366 (M, M+2)

[491] [492] PREPARATION 16: Synthesis of 2-bromo-1-[2S-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

[493] The title compound was prepared in the same manner as in PREPARATION 11. Yield: 66.1%

[494] $^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 3.84 (2H, Abq, $J = 10$Hz), 3.37-3.9 (2H, m), 2.4-2.5 (1H, m), 1.2-2.2 (13H, m)

[495] Mass (m/e) 370, 372 (M, M+2)

[496] [497] PREPARATION 17: Synthesis of 2-bromo-1-[2S-(5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine]-1-yl]-ethanone

[498] The title compound was prepared in the same manner as in PREPARATION 11. Yield: 70%

[499] $^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 3.84 (2H, Abq, $J = 11$Hz), 3.37-3.9 (2H, m), 2.4-2.5 (1H, m), 2.2-2.3 (2H, m), 2.1-2.2 (3H, m), 1.3-1.7 (8H, m), 1.37 (3H, s)

[500] Mass (m/e) 384,386(M, M+2)

[501] [502] PREPARATION 18: Synthesis of 2-bromo-1-[2S-(5-(1-methyl-cyclopropyl)-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine]-1-yl]-ethanone

[503] The title compound was prepared in the same manner as in PREPARATION 11. Yield: 87.7%

[504] $^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 3.82 (2H, Abq, $J = 11$Hz), 3.37-3.9 (2H, m), 2.4-2.5 (1H, m), 2.1-2.2 (3H, m), 1.63 (3H, s), 1.46 (2H, m), 1.05 (2H, m),

[505] Mass (m/e) 342, 344(M, M+2)

[506] [507] PREPARATION 19: Synthesis of
2-bromo-1-[2S-(5-(2,4,6-trimethyl-phenyl)-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

The title compound was prepared in the same manner as in PREPARATION 11.
Yield: 47.4%

$^1$H NMR (CDCl$_3$) $\delta$ 7.0 (2H, s), 5.4-5.5 (1H, m), 3.90 (2H, Abq, $J = 11$Hz), 37-39 (2H, m), 2.4-2.5 (1H, m), 23.6 (3H, s), 233 (6H, s), 2.1-2.2 (3H, m)

Mass (m/e) 406,408(M, M+2)

PREPARATION 20: Synthesis of 3-chloro-1-[2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-propane-1-one

The title compound was prepared in the same manner as in PREPARATION 11.
Yield: 65%

$^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 3.6-3.9 (4H, m), 2.82 (2H, t, $J = 7$ Hz), 2.4-2.5 (1H, m), 2.1-2.2 (3H, m), 1.45 (9H, s)

Mass (m/e) 314 (M+1)

EXAMPLE 1: Synthesis of 2-(adamantane-1-ylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

55 mg (0.18 mmol) of 2-bromo-1-[2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 11 was dissolved in 3 ml of dichloromethane. To this were added 0.10 g (0.73 mmol) of potassium carbonate and 55 mg (0.36 mmol) of 1-adamantaneamine in sequence, followed by stirring for about 5 hours and then isolation and purification through prep-TLC to give 30 mg of title compound in a yield of 44%.

$^1$H NMR (CDCl$_3$) $\delta$ 5.4 (1H, m), 3.6-3.8 (2H, m), 3.46 (2H, s), 2.65 (3H, s), 2.4 (1H, m), 2.0-2.3 (3H, m), 2.1 (3H, br s), 1.7-1.8 (12H, m)

Mass (m/e) 373 (M+1)

EXAMPLE 2: Synthesis of 2-(adamantane-1-ylamino)-1-[2-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

115 mg of the title compound was obtained in a yield of 48% in the same manner as in EXAMPLE 1, except that 197 mg of 2-bromo-1-[2S-(5-ethyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 12 and 188
mg of 1-adamantaneamine were reacted.

\(^1\)H NMR (DMSO) \(\delta\) 5.4-5.6 (1H, m), 3.6-3.8 (2H, m), 3.46 (2H, s), 1.7 (2H, q, J=8Hz), 2.4 (1H, m), 2.0-2.3 (3H, m), 1.9-2.2 (3H, m), 1.6-1.8 (12H, m), 1.4-1.5 (3H, t, J=8Hz)

Mass (m/e) 387

EXAMPLE 3: Synthesis of
2-(adamantane-1-ylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrroldine-1-yl]-ethanone

118 mg of the title compound was obtained in a yield of 75% in the same manner as in EXAMPLE 1, except that 130 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrroldine-1-yl]-ethanone synthesized in PREPARATION 13 and 114 mg of 1-adamantaneamine were reacted.

\(^1\)H NMR (DMSO) \(\delta\) 5.4-5.6 (1H, m), 3.6-3.8 (2H, m), 3.45 (2H, s), 23-25 (1H, m), 1.8-2.2 (6H, m), 1.5-1.8 (12H, m), 1.45 (9H, m)

Mass (m/e) 415

EXAMPLE 4: Synthesis of
2-(cyclopentyl-methyl-amino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrroldine-1-yl]-ethanone

18 mg of the title compound was obtained in a yield of 57% in the same manner as in EXAMPLE 1, except that 30 mg of 2-bromo-1-[2S-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrroldine-1-yl]-ethanone synthesized in PREPARATION 11 and 20 mg of cyclopentylmethylamine were reacted.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 53-5.5 (1H, m), 3.6-4.0 (2H, m), 3.50 (2H,s), 2.6-27 (3H, m), 23-24 (1H, m), 1.8, 24 (3H, m(two singlets)), 0.7-2.1 (12H, m)

Mass (m/e) 321 (M+1)

EXAMPLE 5: Synthesis of
2-(cyclohexyl-methyl-amino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrroldine-1-yl]-ethanone

16.6 mg of the title compound was obtained in a yield of 80% in the same manner as in EXAMPLE 1, except that 180 mg of 2-bromo-1-[2S-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrroldine-1-yl]-ethanone synthesized in PREPARATION 11 and 67 mg of cyclopentylmethylamine were reacted.
[539] ^1^H NMR (CDCl\textsubscript{3}) \( \delta 53-5.5 \) (1H, m), 36-39 (2H, m), 3.50 (2H, s), 2.6-27 (3H, m), 23-24 (1H, m), 23, 26 (3H, m(2 singlets)), 0.7-2.1 (14H, m)

[540] Mass (m/e) 335 (M+1)

[541]


[543] 17 mg of the title compound was obtained in a yield of 33% in the same manner as in EXAMPLE 1, except that 40 mg of 2-bromo-1-[2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethaneone synthesized in PREPARATION 11 and 44 mg of 3-hydroxy-1-adamantaneamine were reacted.

[544] ^1^H NMR (CDCl\textsubscript{3}) \( \delta 53-5.4 \) (1H, m), 37-38 (1H, m), 36-37 (1H, m), 3.45 (2H, s), 2.64 (3H, s), 23-25 (1H, m), 2.2-23 (2H, m), 1.9-2.2 (4H, m), 1.4-1.8 (12H, m)

[545] Mass (m/e) 389 (M+1)

[546]

[547] **EXAMPLE 7: Synthesis of 2-tert-butylamino-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethaneone**

[548] 30 mg of the title compound was obtained in a yield of 68% in the same manner as in EXAMPLE 1, except that 45 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethaneone synthesized in PREPARATION 13 and 27μl of tert-butylamine were reacted.

[549] ^1^H NMR (CDCl\textsubscript{3}) \( \delta 5.4-5.5 \) (1H, m), 37-38 (1H, m), 36-37 (1H, m), 3.45 (2H, m), 2.4-2.5 (1H, m), 20-22 (4H, m), 1.5 (9H, s), 1.1 (9H, s)

[550] Mass (m/e) 337 (M+1)

[551]

[552] **EXAMPLE 8: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-piperidine-1-yl-ethaneone**

[553] 35 mg of the title compound was obtained in a yield of 77% in the same manner as in EXAMPLE 1, except that 45 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethaneone synthesized in PREPARATION 13 and 26 μl of piperidine were reacted.

[554] ^1^H NMR (CDCl\textsubscript{3}) \( \delta 5.4-5.5 \) (1H, m), 3.6-39 (2H, m), 2.8-33 (2H, m), 23-26 (2H, m), 1.9-23 (6H, m), 1.4-1.7 (3H, m), 1.5 (9H, s), 1.15-1.25 (3H, m)

[555] Mass (m/e) 349 (M+1)

[556]
EXAMPLE 9: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(octahydro-quinoline-1-yl)-ethanone

38 mg of the title compound was obtained in a yield of 72% in the same manner as in EXAMPLE 1, except that 45 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 39 µl of decahydroquinoline were reacted.

$^1$H NMR (CDCl$_3$) δ 5.35-5.55 (1H, m), 37-39 (2H, m), 31-34 (2H, m), 1.9-27 (7H, m), 1.0-1.9 (13H, m), 1.5 (9H, m)

Mass (m/e) 403 (M+1)

EXAMPLE 10: Synthesis of 2-(2-amino-1,1-dimethyl-ethalamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

20 mg of 1-[2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-[1,1-dimethyl-2-(trityl-amino)-ethylamino]-ethanone was obtained from PREPARATION 13 in the same manner as in EXAMPLE 1, and the trityl group therein was removed by the use of dichloromethane and trifluoroacetic acid (about 2 ml : 1 ml in volume ratio) and then subjected to Prep-TLC to give 9.5 mg of the title compound in a yield of 37%.

$^1$H NMR (CD OD) δ 5.3-5.4 (1H, m), 38-39 (2H, m), 36-38 (2H, m), 3.54 (2H, s), 274 (2H, Abq, J=12.5Hz), 2.05-2.25 (4H, m), 1.45-1.55 (9H, m), 1.15 (6H, s)

Mass (m/e) 352 (M+1)

EXAMPLE 11: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2,6-dimethyl-piperidine-1-yl)-ethanone

1.5 mg of the title compound was obtained in a yield of 9.0% in the same manner as in EXAMPLE 1, except that 16 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 13 µl of 2,6-dimethylpiperidine were reacted.

$^1$H NMR (CDCl$_3$) δ 5.4-5.5 (1H, m), 36-39 (4H, m), 24-2.5 (2H, m), 20-2.2 (4H, m), 1.6-1.9 (6H, m), 21.48 (9H, s), 1.1-13 (6H, m)

Mass (m/e) 377 (M+1)

EXAMPLE 12: Synthesis of 2-tert-butylamino-1-[2-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
[573] 42 mg of the title compound was obtained in a yield of 43% in the same manner as in EXAMPLE 1, except that 100 mg of 2-bromo-1-[2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 11 and 70 μl of tert-butylamine were reacted.

[574] ¹H NMR (CDCl₃) δ 5.4 (1H, m), 37-38 (1H, m), 36-37 (1H, m), 342 (2H, m), 2.64 (3H, s), 235-2.45 (1H, m), 2.0-2.2 (3H, m), 1.09 (9H, s)

[575] Mass (m/e) 377 (M+1)

[576]

[577] EXAMPLE 13: Synthesis of 2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[578] 62 mg of the title compound was obtained in a yield of 48% in the same manner as in EXAMPLE 1, except that 100 mg of 2-bromo-1-[2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 11 and 111 mg of 4-fluoro-phenyl-1,1-dimethyl-ethylamine were reacted.

[579] ¹H NMR (CDCl₃) δ 7.10 (2H, m), 6.98 (2H, m), 5.4-5.5 (1H, m), 37-38 (1H, m), 36-37 (1H, m), 34-36 (4H, m), 2.67 (3H, s), 2.4-2.5 (1H, m), 2.0-2.2 (3H, m), 1.05 (3H, s), 1.04 (3H, s)

[580] Mass (m/e) 389 (M+1)

[581]

[582] EXAMPLE 14: Synthesis of 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

[583] 26 mg of the title compound was obtained in a yield of 25% in the same manner as in EXAMPLE 1, except that 100 mg of 2-bromo-1-[2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 11 and 59 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

[584] ¹H NMR (CDCl₃) δ 5.4-5.5 (1H, m), 37-38 (1H, m), 36-37 (1H, m), 344 (2H, s), 32(2H, ABq, J=11.5Hz), 2.69 (3H, s), 2.4-2.5 (1H, br s), 2.0-23 (3H, m), 1.07 (3H, s), 1.06 (3H, s)

[585] Mass (m/e) 311 (M+1)

[586]

200 mg of 2-(1,1-dimethyl-2-(trityl-2-aminoethylamino))-1-[2S-(5-methyl-[1,3,4]
oxidazole-2-carbonyl)pyrrolidine-1-yl]-ethanone was obtained from PREPARATION 11 in the same manner as in EXAMPLE 1, and the trityl group therein was removed by the use of dichloromethane and trifluoroacetic acid (about 10 ml : 5 ml in volume ratio), and subjected to Prep-TLC to give 35 mg of the title compound in a yield of 18%.

\[ ^1 \text{H NMR (CD}_3 \text{OD)} \delta 5.4-5.5 \ (1\text{H, m)}, \ 4.18 \ (2\text{H, Abq, J=17Hz)}, \ 3.65-3.8 \ (2\text{H, m)}, \ 3.2-3.3 \ (2\text{H, m)}, \ 2.63 \ (3\text{H, s)}, \ 2.4-2.5 \ (1\text{H, m)}, \ 2.0-2.2 \ (3\text{H, m)} \ 1.50 \ (9\text{H, s)}, \ 1.31 \ (6\text{H, s}) \]

Mass (m/e) 310 (M+1)

EXAMPLE 16: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-pyrrolidine-1-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone

45 mg of the title compound was obtained in a yield of 60% in the same manner as in EXAMPLE 1, except that 60 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 58 mg of 4-fluoro-phenyl-1,1-dimethyl-ethylamine were reacted.

\[ ^1 \text{H NMR (CDCl}_3 \delta 7.10-7.15 \ (2\text{H, m)}, \ 6.98-7.0 \ (2\text{H, m)}, \ 5.4-5.5 \ (1\text{H, m)}, \ 3.7-3.8 \ (1\text{H, m)}, \ 3.6-3.7 \ (1\text{H, m)}, \ 3.4-3.6(2\text{H, m)}, \ 2.65-275 \ (2\text{H, Abq, J=13Hz)}, \ 2.4-2.5 \ (1\text{H, m)}, \ 2.0-2.2 \ (3\text{H, m)}, \ 1.48 \ (9\text{H, s)}, \ 1.06 \ (3\text{H, s)}, \ 1.07 \ (3\text{H, s}) \]

Mass (m/e) 431(M+1)

EXAMPLE 17: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-pyrrolidine-1-yl]-2-[2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino]-ethanone

1.0 mg of the title compound was obtained in a yield of 11.0% in the same manner as in EXAMPLE 1, except that 7 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 8 mg of 2-amino-2-methyl-1-phenyl-propane-1-ol were reacted.

\[ ^1 \text{H NMR (CDCl}_3 \delta 7.20-7.4 \ (5\text{H, m)}, \ 5.35-5.5 \ (1\text{H, m)}, \ 4.3-4.6 \ (1\text{H, m)}, \ 3.6-3.9(2\text{H, m)}, \ 3.5-3.6 \ (2\text{H, m)}, \ 2.4-2.5(1\text{H, m)}, \ 2.0-2.2 \ (3\text{H, m)}, \ 1.4-1.5 \ (9\text{H, m)}, \ 0.9-1.1 \ (6\text{H, m)}) \]

Mass (m/e) 429 (M+1)

EXAMPLE 18: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

1.0 mg of the title compound was obtained in a yield of 10.0% in the same manner as in EXAMPLE 1, except that 8 mg of 2-bromo-1-[2S-(5-tert-butyl-1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 9 mg of 2-amino-1-cyclohexyl-2-methyl-propane-1-ol were reacted.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.4-5.5 (1H, m), 37-38(1H, m), 35-37 (1H, m), 3.46 (2H, s), 30-32 (1H, dd, J = 15, 4Hz) 23-25(1H, m), 2.0-2.2 (3H, m), 1.1-1.9 (11H, m), 1.47 (9H, s), 1.0- 1.5 (6H, m)

Mass (m/e) 435 (M+1)

EXAMPLE 19: Synthesis of 1-[2-(5-tert-butyl-1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamino)-ethanone

1.9 mg of the title compound was obtained in a yield of 133% in the same manner as in EXAMPLE 1, except that 14 mg of 2-bromo-1-[2S-(5-tert-butyl-1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 10 mg of 1-hydroxymethyl-cyclopropylamine were reacted.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.2-4.4 (2H, m), 3.8(1H, d, J = 16 Hz), 3.49(1H, d, J = 16 Hz), 3.5-38(2H, m), 1.7-2.0(4H, m), 1.46 (9H, s), 03-0.7 (4H, m)

Mass (m/e) 351 (M+1)

EXAMPLE 20: Synthesis of N-2-[2-(5-tert-butyl-1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethylamino]-2-methyl-propyl]-methanesulfon amide

160 mg of 2-(2-amino-1,1-dimethyl-ethylamino)-1-[2S-(5-tert-butyl-1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone obtained in EXAMPLE 10 was dissolved in dimethylformamide. To this were added dropwise in sequence 0.18 ml of triethylamine and 0.06 ml of methanesulfonyl chloride at 0°C, the resulting solutin was reacted for about 22 hours, concentrated and then isolated and purified through Prep-TLC to give 9 mg of the title compound in a yield of 4.6%.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.6-5.8 (1H, br) , 5.4-5.5(1H, m), 37-38(1H, m), 35-36(1H, m), 33-35(2H, m), 2.8-30(5H, m), 2.4-2.5(1H,m), 21-23(3H, m), 1.5 (9H, s), 1.15(3H, s), 1.14(3H, s)

Mass (m/e) 430 (M+1)

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EXAMPLE 21: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone

34 mg of the title compound was obtained in a yield of 20.7% in the same manner as in EXAMPLE 1, except that 13.5 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 15 mg of 2-cyclohexyl-1,1-dimethyl-ethylamine were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37-3.8(1H, m), 3.5-3.6(1H, m), 34-3.5(2H, m), 24-2.5 (1H, m), 20-2.2(3H, m), 1.5-1.8(6H, m), 1.49 (9H, s), 1.0-1.4(7H, m), 1.12(3H, s), 1.10(3H, s)

*Mass (m/e) 419 (M+1)

EXAMPLE 22: Synthesis of 2-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethylamino]-2-methyl-propionic acid tert-butyl ester

7.2 mg of the title compound was obtained in a yield of 16.8% in the same manner as in EXAMPLE 1, except that 35 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 32 mg of 2-amino-2-methyl-propionic acid tert-butyl ester were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37-3.8(1H, m), 3.5-3.6(1H, m), 339 (2H, Abq, J = 12Hz), 2.4-2.5 (1H, m), 20-2.2(3H, m), 1.47(9H, s), 1.45 (9H, s), 1.29(6H, s)

Mass (m/e) 423 (M+1)

EXAMPLE 23: Synthesis of 2-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethylamino]-2-methyl-propionic acid

1.5 ml of trifluoroacetic acid and a catalytic amount of triethylsilane were added dropwise to 4.5 mg of 2-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethylamino]-2-methyl-propionic acid tert-butyl ester synthesized in EXAMPLE 22 in the presence of dichloromethane, allowed to react for about 1.5 hours, concentrated, and then isolated and purified by Prep-TLC to give 2.4 mg of the title compound in a yield of 60%.

Mass (m/e) 367 (M+1)

EXAMPLE 24: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
0.6 mg of the title compound was obtained in a yield of 5.5% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 88 mg of (1-amino-cyclopentyl)-methanol were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37.38(1H, m), 36-37(1H, m), 3.4-3.5 (2H, br s), 32-33 (2H, br s), 2.4-2.5 (1H, m), 2.0-2.2(3H, m), 13-1.8 (8H, m), 1.48(9H, s)

Mass (m/e) 379 (M+1)

EXAMPLE 25: Synthesis of 2-tert-butylamino-1-[2-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

9 mg of the title compound was obtained in a yield of 20% in the same manner as in EXAMPLE 1, except that 45 mg of 2-bromo-1-[2S-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 15 and 39 μl of tert-butylamine were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 8.13 (2H, d, J = 7.5 Hz), 7.4-7.7 (3H, m), 37-38(1H, m), 36-37(1H, m), 3.5 (2H, m), 2.4-2.5 (1H, m), 2.0-2.2(3H, m), 1.12(9H, s)

Mass (m/e) 357 (M+1)

EXAMPLE 26: Synthesis of 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

9 mg of the title compound was obtained in a yield of 19.6% in the same manner as in EXAMPLE 1, except that 45 mg of 2-bromo-1-[2S-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 15 and 35 μl of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 8.13 (2H, d, J = 8 Hz), 7.4-7.8 (3H, m), 36-38(2H, m), 3.49 (2H, m), 32-33(2H, m), 2.4-2.5 (1H, m), 2.0-2.2(3H, m), 1.0-1.1(6H, m)

$^1$H NMR (CDCl$_3$) $\delta$ 8.17 (2H, d, J = 8 Hz), 7.63 (1H, t, J = 8 Hz), 7.53 (2H, t, J = 8 Hz), 5.4-5.5 (1H, m), 37-38(1H, m), 36-37(1H, m), 3.47 (2H, m), 3.2 (2H, s), 2.4-2.5 (1H, m), 2.1-2.2(3H, m), 1.06(6H, s)

Mass (m/e) 373 (M+1)

EXAMPLE 27: Synthesis of 2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
28 mg of the title compound was obtained in a yield of 58.6% in the same manner as in EXAMPLE 1, except that 45 mg of 2-bromo-1-[2S-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 15 and 25 mg of 2-methoxy-1,1-dimethyl-ethylamine were reacted.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 8.17 (2H, d, J = 8 Hz), 7.61 (1H, t, J = 8 Hz), 7.54 (2H, t, J = 8 Hz), 5.4-5.5 (1H, m), 3.7-38(1H, m), 3.6-37(1H, m), 3.47 (2H, m), 3.34 (3H, s), 3.18 (2H, s), 2.4-2.5 (1H, m), 2.1-2.2(3H, m), 1.07(6H, s) \]

Mass (m/e) 387 (M+1)

EXAMPLE 28: Synthesis of 2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

17 mg of the title compound was obtained in a yield of 33% in the same manner as in EXAMPLE 1, except that 45 mg of 2-bromo-1-[2S-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 15 and 33 mg of 2-methoxymethoxy-1,1-dimethyl-ethylamine were reacted.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 8.17 (2H, d, J = 8 Hz), 7.59 (1H, t, J = 8 Hz), 7.54 (2H, t, J = 8 Hz), 5.4-5.5 (1H, m), 4.61 (2H, s), 3.7-38(1H, m), 3.6-37(1H, m), 3.47 (2H, m), 3.35 (3H, s), 2.4-2.5 (1H, m), 2.1-2.2(3H, m), 1.09(6H, s) \]

Mass (m/e) 417 (M+1)

EXAMPLE 29: Synthesis of 2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

13 mg of the title compound was obtained in a yield of 48.4% in the same manner as in EXAMPLE 1, except that 25 mg of 2-bromo-1-[2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 11 and 17 mg of 2-methoxy-1,1-dimethyl-ethylamine were reacted.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 5.3-5.4 (1H, m), 3.7-38(1H, m), 3.6-37(1H, m), 3.42 (2H, ABq, J = 16 Hz ), 3.3 (3H, s), 3.16 (2H, s), 2.61 (3H, s), 2.3-2.4 (1H, m), 2.0-2.2(3H, m), 1.04 (6H, s) \]

Mass (m/e) 325 (M+1)

EXAMPLE 30: Synthesis of 2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-
2-carbonyl)-pyrrolidine-1-yl]-ethanone

[663] 10 mg of the title compound was obtained in a yield of 34.1% in the same manner as in EXAMPLE 1, except that 25 mg of 2-bromo-1-[2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 11 and 22 mg of 2-methoxymethoxy-1,1-dimethyl-ethyamine were reacted.

[664] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 53-5.4 (1H, m), 4.6 (2H, s), 37-38 (1H, m), 3.6-37 (1H, m), 3.42 (2H, ABq, J = 14 Hz), 331 (3H, s), 329 (2H, q, J = 7 Hz), 2.61 (3H, s), 23-24 (1H, m), 2.0-2.2 (3H, m), 1.08 (6H, s)

[665] Mass (m/e) 355 (M+1)

[666]

[667] EXAMPLE 31: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethy lamino)-ethanone

[668] 16.4 mg of the title compound was obtained in a yield of 77.0% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 17 mg of 2-methoxy-1,1-dimethyl-ethyamine were reacted.

[669] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 53-5.4 (1H, m), 37-38 (1H, m), 3.6-37 (1H, m), 3.42 (2H, ABq, J = 16 Hz), 331 (3H, s), 3.16 (2H, s), 23-2.4 (1H, m), 2.0-2.2 (3H, m), 1.45 (9H, s), 1.04 (6H, s)

[670] Mass (m/e) 367 (M+1)

[671]

[672] EXAMPLE 32: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethy lamino)-ethanone

[673] 13.8 mg of the title compound was obtained in a yield of 60.0% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 15.5 mg of 2-methoxymethoxy-1,1-dimethyl-ethyamine were reacted.

[674] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.5-5.6 (1H, m), 4.59 (2H, s), 37-38 (1H, m), 3.6-37 (1H, m), 3.43 (2H, ABq, J = 14 Hz), 332 (3H, s), 331 (2H, ABq, J = 10 Hz), 23-2.4 (1H, m), 2.0-2.2 (3H, m), 1.44 (9H, s), 1.07 (6H, s)

[675] Mass (m/e) 397 (M+1)

[676]

[677] EXAMPLE 33: Synthesis of 2-tert-butylamino-1-[2-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
[678] 15.7 mg of the title compound was obtained in a yield of 80.2% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[2S-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethane synthesized in PREPARATION 16 and 8 mg of tert-butylamine were reacted.

[679] $^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37-38 (1H, m), 35-36 (1H, m), 341 (2H, ABq, J = 16 Hz), 29-30 (1H, m), 2.4-2.5 (1H, m), 1.2-2.1 (13H, m), 1.08 (9H, s).

[680] Mass (m/e) 363 (M+1)

[681]

[682] EXAMPLE 34: Synthesis of 1-[2-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethane

[683] 12.2 mg of the title compound was obtained in a yield of 60.0% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[2S-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethane synthesized in PREPARATION 16 and 9.7 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

[684] $^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37-38 (1H, m), 355-365 (1H, m), 341 (2H, s), 315 (2H, ABq, J = 12 Hz), 29-30 (1H, m), 2.4-2.5 (1H, m), 1.2-2.2 (13H, m), 1.04 (3H, s), 1.02(3H, s).

[685] Mass (m/e) 379 (M+1)

[686]

[687] EXAMPLE 35: Synthesis of 1-[2-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethane

[688] 16.8 mg of the title compound was obtained in a yield of 79.2% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[2S-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethane synthesized in PREPARATION 16 and 15.9 mg of 2-methoxy-1,1-dimethyl-ethylamine were reacted.

[689] $^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37-38 (1H, m), 355-365 (1H, m), 344 (2H, ABq, J = 14 Hz), 330 (3H, s), 317 (2H, s), 29-30 (1H, m), 23-24 (1H, m), 1.2-2.2 (13H, m), 1.05 (3H, s), 1.04(3H, s)

[690] Mass (m/e) 393 (M+1)

[691]


[693] 20.1 mg of the title compound was obtained in a yield of 880% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[2S-(5-cyclohexyl-[1,3,4]
oxadiazole-2-carbonyl)-pyrrolidin-1-yl)-ethanone synthesized in PREPARATION 16 and 14.4 mg of 2-methoxymethoxy-1,1-dimethyl-ethylamine were reacted.

\[ 1H \text{ NMR (CDCl}_3\text{) } \delta \ 5.4-5.5 \ (1H, m), \ 4.59 \ (2H, s), \ 3.7-3.8 \ (1H, m), \ 3.55-3.65 \ (1H, m), \ 3.42 \ (2H, Abq, J = 15 Hz), \ 3.33 \ (2H, Abq, J = 12 Hz), \ 3.32 \ (3H, s), \ 2.9-3.0 \ (1H, m), \ 2.3-2.4 \ (1H, m), \ 1.2-2.2 \ (13H, m), \ 1.07 \ (6H, s) \]

Mass (m/e) 423 (M+1)

EXAMPLE 37: Synthesis of 2-(2-benzyloxy-1,1-dimethyl-ethylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidin-1-yl]-ethanone

173 mg of the title compound was obtained in a yield of 673% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidin-1-yl]-ethanone synthesized in PREPARATION 13 and 21 mg of 2-benzyloxy-1,1-dimethyl-ethylamine were reacted.

\[ 1H \text{ NMR (CDCl}_3\text{) } \delta \ 7.2-7.4 \ (5H, m), \ 5.34-5.4 \ (1H, m), \ 4.50 \ (2H, s), \ 3.7-3.8 \ (1H, m), \ 3.55-3.65 \ (1H, m), \ 3.41 \ (2H, Abq, J = 16 Hz), \ 3.27 \ (2H, s), \ 2.3-2.4 \ (1H, m), \ 2.0-2.2 \ (3H, m), \ 1.46 \ (9H, s), \ 1.1 \ (3H, s), \ 1.08 \ (3H, s) \]

Mass (m/e) 443 (M+1)

EXAMPLE 38: Synthesis of 2-(2-benzyloxy-1,1-dimethyl-ethylamino)-1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidin-1-yl]-ethanone

14.2 mg of the title compound was obtained in a yield of 56.1% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[2S-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidin-1-yl]-ethanone synthesized in PREPARATION 16 and 193 mg of 2-benzyloxy-1,1-dimethyl-ethylamine were reacted.

\[ 1H \text{ NMR (CDCl}_3\text{) } \delta \ 7.2-7.4 \ (5H, m), \ 5.3-5.4 \ (1H, m), \ 4.53 \ (2H, s), \ 3.7-3.8 \ (1H, m), \ 3.55-3.65 \ (1H, m), \ 3.44 \ (2H, Abq, J = 16 Hz), \ 3.26 \ (2H, s), \ 2.9-3.0 \ (1H, m), \ 2.3-2.4 \ (1H, m), \ 1.2-2.2 \ (13H, m), \ 1.1 \ (3H, s), \ 1.08 \ (3H, s) \]

Mass (m/e) 469 (M+1)

EXAMPLE 39: Synthesis of 2-tert-butylamino-1-[2-[5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidin-1-yl]-ethanone

3.2 mg of the title compound was obtained in a yield of 327% in the same manner
as in EXAMPLE 1, except that 10 mg of
2-bromo-1-[2S-(5-(1-methyl-cyclohexyl)\-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 17 and 4 mg of tert-butylamine were reacted.

[709] \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 5.4-5.5 (1H, m), 37-38 (1H, m), 36-37 (1H, m), 345 (2H, Abq, \( J = 16 \) Hz), 2.4-2.5 (1H, m), 22-23 (2H, m), 2.0-2.15 (3H, m), 13-1.7 (8H, m), 1.37 (3H, s), 1.05 (9H, s)

[710] Mass (m/e) 377 (M+1)

[711]

EXAMPLE 40: Synthesis of
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2S-(5-(1-methyl-cyclohexyl)\-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[712] 2.2 mg of the title compound was obtained in a yield of 21.5% in the same manner as in EXAMPLE 1, except that 10 mg of
2-bromo-1-[2S-(5-(1-methyl-cyclohexyl)\-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 17 and 4.6 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

[713] \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 5.4-5.5 (1H, m), 37-38 (1H, m), 35-37 (1H, m), 343 (2H, Abq, \( J = 15 \) Hz), 3.16 (2H, Abq, \( J = 11 \) Hz), 2.4-2.5 (1H, m), 22-23 (2H, m), 2.0-2.15 (3H, m), 13-1.7 (8H, m), 1.37 (3H, s), 1.05 (3H, s), 1.04 (3H, s)

[714] Mass (m/e) 393 (M+1)

[715]

EXAMPLE 41: Synthesis of
2-(1-hydroxymethyl-cyclopentylamino)-1-[2S-(5-(1-methyl-cyclohexyl)\-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[716] 34 mg of the title compound was obtained in a yield of 31.2% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[2S-(5-(1-methyl-cyclohexyl)\-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 17 and 6 mg of 1-hydroxymethyl-cyclopentylamine were reacted.

[717] \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 5.4-5.5 (1H, m), 37-38 (1H, m), 35-37 (1H, m), 342 (2H, s), 3.19 (2H, Abq, \( J = 11 \) Hz), 2.4-2.5 (1H, m), 22-23 (2H, m), 2.0-2.15 (3H, m), 13-1.8 (18H, m), 1.38 (3H, s)

[718] Mass (m/e) 419 (M+1)

[719]

[720]

[721]
EXAMPLE 42: Synthesis of 2-tert-butyramino-1-[2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

4.5 mg of the title compound was obtained in a yield of 46.0% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[(S)-5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 14 and 4 mg of tert-butyramine were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37-3.8 (1H, m), 36-37 (1H, m), 345 (2H, Abq, J = 16 Hz), 2.4-2.5 (1H, m), 20-22 (3H, m), 1.8 (2H, q, J = 7.5 Hz), 1.43 (6H, s), 1.09 (9H, s), 0.85 (3H, t, J = 7.5 Hz)

Mass (m/e) 351 (M+1)

EXAMPLE 43: Synthesis of 1-[2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

0.5 mg of the title compound was obtained in a yield of 4.9% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[(S)-2-(5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 14 and 5 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37-3.8 (1H, m), 36-37 (1H, m), 333 (2H, br s), 33 (2H, Abq, J = 13 Hz), 2.4-2.5 (1H, m), 20-22 (3H, m), 1.8 (2H, q, J = 7 Hz), 1.41 (6H, s), 1.06 (3H, s), 1.04 (3H, s), 0.83 (3H, t, J = 7 Hz)

Mass (m/e) 367 (M+1)

EXAMPLE 44: Synthesis of 1-[2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

4.1 mg of the title compound was obtained in a yield of 37.4% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[(S)-2-(5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 14 and 6.4 mg of 1-hydroxymethyl-cyclopentylamine were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37-3.8 (1H, m), 35-3.6 (1H, m), 341 (2H, s),
3.2 (2H, Abq, J = 12 Hz), 2.4-2.5 (1H, m), 2.0-2.2 (3H, m), 1.8 (2H, q, J = 7.5 Hz), 1.4-1.8 (8H, m), 1.42 (6H, s), 0.85 (3H, t, J = 7.5 Hz)

[735] Mass (m/e) 393 (M+1)

[736]

[737] EXAMPLE 45: Synthesis of 2-tert-butylamino-1-[2-[5-(1-methyl-cyclopropyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[738] 5.1 mg of the title compound was obtained in a yield of 52.2% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[2S-(5-(1-methyl-cyclopropyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 18 and 43 mg of tert-butylamine were reacted.

[739] ¹H NMR (CDCl₃) δ 53.5-5.4 (1H, m), 37-38 (1H, m), 36-37 (1H, m), 3.41 (2H, Abq, J = 15 Hz), 2.3-2.5 (1H, m), 2.0-2.2 (3H, m), 1.59 (3H, s), 1.41 (2H, m), 1.1 (9H, s), 1.03 (2H, m)

[740] Mass (m/e) 335 (M+1)

[741]


[743] 6.0 mg of the title compound was obtained in a yield of 58.6% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[2S-(5-(1-methyl-cyclopropyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 18 and 5.2 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

[744] ¹H NMR (CDCl₃) δ 53.5-5.4 (1H, m), 37-38 (1H, m), 35-37 (1H, m), 3.41 (2H, s), 3.14 (2H, Abq, J = 12 Hz), 3.16 (2H, Abq, J = 11 Hz), 2.4-2.5 (1H, m), 2.0-2.2 (3H, m), 1.59 (3H, s), 1.43 (2H, m), 1.02-1.04 (2H, m), 1.04 (3H, s), 1.03 (3H, s)

[745] Mass (m/e) 351 (M+1)

[746]


[748] 5.8 mg of the title compound was obtained in a yield of 52.7% in the same manner as in EXAMPLE 1, except that 10 mg of
2-bromo-1-[2S-(5-(1-methyl-cyclopropyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 18 and 6.7 mg of 1-hydroxymethyl-cyclopentylamine were reacted.

\([749]\)

$^1\text{H NMR (CDCl}_3\) \delta 53-5.4 (1H, m), 39-4.1 (1H, m), 35-38 (3H, m), 339 (2H, s), 3.19 (2H, Abq, J = 11.5 Hz), 23-25 (1H, m), 20-22 (3H, m), 1.4-1.8 (10H, m), 1.57 (3H, s), 1.04 (2H, m)

\([750]\)

Mass (m/e) 377 (M+1)

\([751]\)

**EXAMPLE 48: Synthesis of**

2-tert-butylamino-1-[2-[5-(2,4,6-trimethyl-phenyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

\([753]\)

7.0 mg of the title compound was obtained in a yield of 71.4% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[2S-(5-(2,4,6-trimethyl-phenyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 19 and 3.6 mg of tert-butylamine were reacted.

\([754]\)

$^1\text{H NMR (CDCl}_3\) \delta 6.96 (2H, s), 5.4-5.5 (1H, m), 37-38 (1H, m), 36-37 (1H, m), 3.45 (2H, Abq, J = 16 Hz), 24-25 (1H, m), 23(3H, s), 22.8(6H, s), 20-22 (3H, m), 1.1 (9H, s)

\([755]\)

Mass (m/e) 399 (M+1)

\([756]\)

**EXAMPLE 49: Synthesis of**

2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2,4,6-trimethyl-phenyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

\([758]\)

13 mg of the title compound was obtained in a yield of 127% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[2S-(5-(2,4,6-trimethyl-phenyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 19 and 4.4 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

\([759]\)

$^1\text{H NMR (CDCl}_3\) \delta 6.97 (2H, s), 5.4-5.5 (1H, m), 37-38 (1H, m), 36-37 (1H, m), 3.46 (2H, s), 3.18 (2H, Abq, J = 11 Hz), 24-25 (1H, m), 233(3H, s), 23(6H, s), 20-22 (3H, m), 1.06 (3H, s), 1.05 (3H, s)

\([760]\)

Mass (m/e) 415 (M+1)

\([761]\)

**EXAMPLE 50: Synthesis of**
2-(1-hydroxymethyl-cyclopentylamino)-1-[2-[5-(2,4,6-trimethyl-phenyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[763] 4.0 mg of the title compound was obtained in a yield of 36.9% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[2S-(5-(2,4,6-trimethyl-phenyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 19 and 57 mg of 1-hydroxymethyl-cyclopentylamine were reacted.

[764] $^1$H NMR (CDCl$_3$) $\delta$ 6.96 (2H, s), 5.4-5.5 (1H, m), 3.5-4.2 (6H, m), 2.4-2.5 (1H, m), 233(3H, s), 231(6H, s), 1.6-2.2 (8H, m)

[765] Mass (m/e) 441 (M+1)

EXAMPLE 51: Synthesis of 1-[2-[5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-[(2-hydroxy-ethyl)-methyl-amino]-ethanone

[768] 37 mg of the title compound was obtained in a yield of 753% in the same manner as in EXAMPLE 1, except that 50 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 35 µl of (2-hydroxy-ethyl)-methyl-amine were reacted.

[769] $^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.6 (1H, m), 30-4.0 (6H, m), 27-2.8(2H, br s), 2.5 (3H, br s), 23-24 (1H, m), 2.0-2.2(3H, m), 1.48 (9H, m)

[770] Mass (m/e) 339 (M+1)

EXAMPLE 52: Synthesis of 3-tert-butylamino-1-[2-[5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-propane-1-one

[773] 6.7 mg of the title compound was obtained in a yield of 20.0% in the same manner as in EXAMPLE 1, except that 30 mg of 3-chloro-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-propane-1-one synthesized in PREPARATION 20 and 27 µl of tert-butylamine were reacted.

[774] $^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 37-38 (1H, m), 36-37 (1H, m), 29-30 (2H, m), 2.6-2.8 (2H, m), 2.4-2.5 (1H, m), 2.0-2.2 (3H, m), 1.46 (9H, s), 1.18 (9H, s)

[775] Mass (m/e) 351 (M+1)

EXAMPLE 53: Synthesis of 1-[2-[5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-3-[(2-hydroxy-ethyl)-methyl-amino]-propane-1-one

[778] 10.9 mg of the title compound was obtained in a yield of 323% in the same manner as in EXAMPLE 1, except that 30 mg of 3-chloro-1-[2S-(5-tert-butyl-[1,3,4]
oxadiazole-2-carbonyl)-pyrrolidine-1-yl)-propane-1-one synthesized in
PREPARATION 20 and 23 µl of (2-hydroxy-ethyl)-methyl-amine were reacted.

[779] 

$^1$H NMR (CDCl$_3$) δ 5.4-5.5 (1H, m), 37-38 (1H, m), 35-37 (3H, m), 27-28 (1H, m), 26-27 (1H, m), 2.45-2.55 (4H, m), 235-245 (1H, m), 2.25 (3H, m), 2.0-2.2 (3H, m), 1.45 (9H, s)

[780] Mass (m/e) 353 (M+1)

[781]

[782] EXAMPLE 54: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-pyrrolidine-1-yl]-3-[2-hydroxymethyl-piperidine-1-yl]-propane-1-one

[783] 19.4 mg of the title compound was obtained in a yield of 51.7% in the same
manner as in EXAMPLE 1, except that 30 mg of 3-chloro-1-[2S-(5-tert-butyl-[1,3,4]
oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-propane-1-one synthesized in
PREPARATION 20 and 33 mg of 2-hydroxy-methyl-piperidine were reacted.

[784] $^1$H NMR (CDCl$_3$) δ 535-5.45 (1H, m), 34-39 (3H, m), 29-34 (3H, m), 23-28 (3H, m), 2.2-23 (1H, m), 2.0-2.2 (3H, m), 1.2-1.7 (6H, m), 1.45 (9H, s)

[785] Mass (m/e) 393 (M+1)

[786]

[787] EXAMPLE 55: Synthesis of 6-(2-[2-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propylamino)-pyridine
-3-sulfonic acid dimethylamide

[788] 10 mg of the title compound was obtained in a yield of 643% in the same manner
as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4]
oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 13
and 24 mg of 6-(2-amino-2-methyl-propylamino)-pyridine-3-sulfonic acid
dimethylamide were reacted.

[789] $^1$H NMR (CDCl$_3$) δ 840 (1H, s), 7.60 (1H, d, J = 8.5 Hz), 6.43 (1H, d, J = 9.0 Hz),
6.04 (1H, br t), 5.4-5.5 (1H, m), 37-38 (1H, m), 35-36 (1H, m), 343 (2H, Abq, J =
12 Hz), 32-34 (2H, m), 2.67 (6H, s), 2.4-2.5 (1H, m), 20-2.2(3H, m), 1.45 (9H, s),
1.12 (3H, s), 1.11 (3H, s)

[790] Mass (m/e) 536 (M+1)

[791]

[792] EXAMPLE 56: Synthesis of 6-(2-[3-[2-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-pyrrolidine-1-yl]-3-oxo-propylamino]-2-methyl-propylamino)-pyridine
-3-sulfonic acid dimethylamide
1.4 mg of the title compound was obtained in a yield of 80% in the same manner as in EXAMPLE 1, except that 10 mg of 3-chloro-1-[2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-propane-1-one synthesized in PREPARATION 13 and 26 mg of 6-(2-amino-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide were reacted.

$^1$H NMR (CDCl$_3$) δ 8.39 (1H, s), 7.58 (1H, d, J = 10 Hz), 6.40 (1H, d, J = 85 Hz), 5.4-5.5 (1H, m), 3.73-3.8 (1H, m), 2.35-2.6 (1H, m), 3.45 (2H, m), 2.8-3.0 (2H, d), 2.68 (6H, s), 2.4-2.5 (1H, m), 2.0-2.2 (3H, m), 1.25 (9H, s), 1.15 (6H, s)

Mass (m/e) 550 (M+1)

EXAMPLE 57: Synthesis of 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-3-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-propane-1-one

1.0 mg of the title compound was obtained in a yield of 67% in the same manner as in EXAMPLE 1, except that 10 mg of 3-chloro-1-[2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-propane-1-one synthesized in PREPARATION 13 and 18 mg of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine synthesized by a method as disclosed in WO03/004498 were reacted.

$^1$H NMR (CDCl$_3$) δ 5.4-5.5 (1H, m), 4.13 (2H, t, J = 5.5 Hz), 3.91 (2H, s), 3.73-3.8 (1H, m), 3.6-3.7 (1H, m), 2.9-3.1 (4H, m), 2.5-2.7 (2H, m), 2.25-2.5 (1H, m), 2.0-2.2 (3H, m), 1.46 (9H, s), 2.45 (2H, m), 2.8-3.0 (2H, m), 2.68 (6H, s), 2.4-2.5 (1H, m), 2.0-2.2 (3H, m), 1.25 (9H, s), 1.15 (6H, s)

Mass (m/e) 470 (M+1)

EXAMPLE 58: Synthesis of 1-[1-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-[1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamino]ethanone

5.2 mg of the title compound was obtained in a yield of 44% in the same manner as in EXAMPLE 1, except that 9.5 mg of 2-bromo-1-[(S)-2-5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 14 and 13 mg of 1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamino synthesized by a method as disclosed in WO 02/051836 were reacted.

$^1$H NMR (CDCl$_3$) δ 8.06-8.01 (m, 1H), 7.39-7.32 (m, 1H), 6.55-6.49 (m, 1H),
6.43-639 (m, 1H), 5.43-5.40 (m, 1H), 5.12 (br s, 1H), 3.73-3.68 (m, 1H), 3.59-3.54 (m, 1H), 3.41 (s, 2H), 3.26-3.15 (m, 2H), 2.43-2.37 (m, 1H), 2.15-2.04 (m, 3H), 1.82-1.75 (m, 8H), 1.42-1.38 (m, 6H), 1.13 (s, 6H), 0.87-0.81 (m, 6H).

[805]
Mass (m/e) 443 (M+1)

[806]
PREPARATION 21: Synthesis of (S)-2-[(5-tert-butyl-[1,3,4] oxadiazole-2-yl)-hydroxy-methyl]-2-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester

[807]
0.46 ml of n-butyllithium (2.5M in hexane solution) was slowly added dropwise to a solution of 143 mg (1.14 mmol) of 2-tert-butyl-[1,3,4]-oxadiazole in 10 ml of anhydrous tetrahydrofuran maintained at -78°C. To the resulting solution, a solution of 110 mg (0.52 mmol) of (S)-2-formyl-2-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester in 8 ml of anhydrous tetrahydrofuran was added dropwise for about 5 minutes, while the same temperature being kept. The reaction mixture was slowly raised to room temperature over a period of 3 hours while stirring. After stirring at room temperature for 1 hour, 100 ml of ethyl acetate was added thereto, washed with aqueous saturated ammonium chloride and aqueous NaCl in sequence. The organic layer obtained was dried over anhydrous magnesium sulfate, filtered off and concentrated under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 3) to give 152 mg of the title compound in a yield of 87%.

[809]

1H NMR (CDCl3) δ 6.59 (d, 1H, 4Hz), 5.18 (s, 1H), 3.56-3.53 (m, 1H), 3.29-3.26 (m, 1H), 1.89-1.67 (m, 4H), 1.60-1.54 (m, 4H), 1.48-1.37 (m, 18H).

[810]
Mass (m/e) 340 (M+1)

[811]
PREPARATION 22: Synthesis of (S)-2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-2-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester

[812]
152 mg (0.45 mmol) of (2S,4S)-2-[(1-ethoxy-ethoxy)-[5-(1-methyl-cyclohexyl]-[1,2,4]oxadiazole-3-yl]-methyl 1]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester obtained in PREPARATION 21 was dissolved in 10 ml of methylene chloride, and 5 ml of Dess-Martin periodonane (15% methylene chloride) was added dropwise thereto at room temperature. After stirring for 2 hours at room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 3 : 1) to give 147 mg of the title compound in a yield of 97%.

[814]

1H NMR (CDCl3) δ 3.87-3.82 (m, 1H), 3.74-3.60 (m, 1H), 2.64-2.68 (m, 2H), 2.16-2.10 (m, 2H), 1.91-1.81 (m, 1H), 1.69 (d, 3H, 9Hz), 1.48-1.44 (m, 9H),
1.27-1.20 (m, 9H).

[815] Mass (m/e) 338 (M+1)

[816]

[817] **PREPARATION 23: Synthesis of 2-bromo-1-[(S)-2-[5-tert-butyl-\[1,3,4\]oxadiazole-2-carbonyl]-2-methyl-pyrrolidine-1-yl]-ethanone**

[818] 115 mg of the title compound was obtained in a yield of 74% in the same manner as in PREPARATION 11, except that 147 mg (0.44 mmol) of (S)-2-[(5-tert-butyl-\[1,3,4\]oxadiazole-2-carbonyl]-2-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester as synthesized in PREPARATION 22, 8 ml of 3N HCl/methyl acetate, 60 \(\mu\)l (0.65 mmol) of bromoacetyl bromide and 167 \(\mu\)l (0.96 mmol) of N,N-diisopropylethylamine were used.

[819] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.08-3.85 (m, 3H), 379-367 (m, 2H), 2.53-2.48 (m, 1H), 231-227 (m, 2H), 1.90-1.86 (m, 1H), 1.66-1.64 (m, 3H), 1.46-1.28 (m, 9H).

[820] Mass (m/e) 358, 360 (M, M+2)

[821] Mass (m/e) 362 (M+1)

[822]

[823] **EXAMPLE 59: Synthesis of 2-tert-butylamino-1-\[(2S)-(5-tert-butyl-\[1,3,4\]oxadiazole-2-carbonyl]-2-methyl-pyrrolidine-1-yl]-ethanone**

[824] 10.4 mg of the title compound was obtained in a yield of 63% in the same manner as in EXAMPLE 1, except that 17.0 mg (0.048 mmol) of 2-bromo-1-\[(S)-2-[5-tert-butyl-\[1,3,4\]oxadiazole-2-carbonyl]-2-methyl-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 23 and 17.0 mg (0.142 mmol) of tert-butylamine were reacted.

[825] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.00-3.93 (m, 1H), 375-370 (m, 1H), 340-314 (m, 2H), 2.53-2.45 (m, 1H), 230-217 (m, 2H), 2.07 (br s, 1H), 1.86-1.81 (m, 1H), 1.63 (s, 3H), 1.44 (s, 9H), 0.99 (s, 9H).

[826] Mass (m/e) 351 (M+1)

[827]

[828] **EXAMPLE 60: Synthesis of 1-\[(2S)-(5-tert-butyl-\[1,3,4\]oxadiazole-2-carbonyl]-2-methyl-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone**

[829] 11.6 mg of the title compound was obtained in a yield of 57% in the same manner as in EXAMPLE 1, except that 20.0 mg (0.056 mmol) of 2-bromo-1-\[(S)-2-[5-tert-butyl-\[1,3,4\]oxadiazole-2-carbonyl]-2-methyl-pyrrolidine-1-yl]
[830] 1-H NMR (CDCl₃) δ 4.01-3.94 (m, 1H), 3.71-3.66 (m, 1H), 3.36-3.16 (m, 2H), 2.96-2.75 (m, 2H), 2.56-2.48 (m, 1H), 2.34-2.19 (m, 2H), 2.00 (br s, 1H), 1.88-1.83 (m, 1H), 1.63 (s, 3H), 1.46 (s, 9H), 0.98 (s, 3H), 0.92 (s, 3H).

[831] Mass (m/e) 366 (M+1)

[832]


[834] 0.283 g (1.21 mmol) of 4S-fluoro-pyrrolidine-1,2S-dicarboxylic acid 1-tert-butylester and 0.118 g (1.21 mmol) of methoxymethylamine were dissolved in dimethylformamide. To the solution, were added 0.302 g (1.57 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbo-di-imide hydrochloride (HDC) and 0.213 g (1.57 mmol) of 1-hydroxybenzotriazolole hydrate (HOBT), and 0.68 ml (4.8 mmol) of triethylamine was added dropwise. Then the solution was stirred for 23 hours. The reaction was diluted with excess ethyl acetate, and the product was washed once with aqueous 1N HCl and aqueous NaCl, respectively, and dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate = 1 : 2) to give 0.234 g of the title compound in a yield of 70%.

[835] 1-H NMR (CDCl₃) δ 5.1-5.3 (1H, m), 4.6-4.8 (1H, m), 3.7-3.95 (2H, m), 37-38 (3H, m), 3.21 (3H, s), 2.2-2.6 (2H, m), 1.4-1.6 (9H, m)

[836] Mass (m/e) 277 (M+1)

[837]


[839] 0.214 g (2.54 mmol) of 2-methyl-1,3,4-oxadiazole was dissolved in tetrahydrofuran, and the temperature of a reactor was cooled to -78°C. To this was slowly added dropwise 1.02 ml of butyllithium (2.5M in hexane), followed by stirring for 40 minutes. Thereafter, 0.656 g (2.54 mmol) of magnesium bromide ethylether complex was added and then stirred for 40 minutes. To this was slowly added dropwise a solution of 0.234 g (0.85 mmol) of 4S-fluoro-2S-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester in tetrahydrofuran, followed by slowly warming to room temperature. After stirring for about 3 hours, the product was diluted with ethyl
acetate, washed once with aqueous saturated ammonium chloride solution and aqueous NaCl solution, respectively, dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 1) to give 77 mg of the title compound in a yield of 30%.

\[840\]  
$^1$H NMR (CDCl$_3$) $\delta$ 5.1-5.4 (2H, m), 3.65-4.0 (2H, m), 2.6-2.8 (4H, m), 2.2-2.4 (1H, m), 13-1.5 (9H, m)

\[841\]
Mass (m/e) 300 (M+1)

\[842\]

\[843\] PREPARATION 26: Synthesis of 4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound was synthesized in the same manner as in PREPARATION 2. Yield: 82.9%

\[845\]  
$^1$H NMR (CDCl$_3$) $\delta$ 5.2-5.5 (2H, m), 37-4.0 (2H, m), 2.6-2.8 (2H, m), 1.7 (2H, q, J = 7 Hz), 13-1.4 (6H, m), 0.9 (3H, t, J = 7 Hz)

\[846\]
Mass (m/e) 356 (M+1)

\[847\]

\[848\] PREPARATION 27: Synthesis of 4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound was synthesized in the same manner as in PREPARATION 2. Yield 43%

\[850\]  
$^1$H NMR (CDCl$_3$) $\delta$ 5.2-5.5 (2H, m), 37-4.0 (2H, m), 2.6-2.8 (2H, m), 13-1.5 (18H, m)

\[851\]
Mass (m/e) 342 (M+1)

\[852\]

\[853\] PREPARATION 28: Synthesis of 4S-fluoro-2S-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound was synthesized in the same manner as in PREPARATION 2. Yield 42%

\[855\]  
$^1$H NMR (CDCl$_3$) $\delta$ 80-82 (2H, m), 7.5-77 (3H, m), 5.2-5.5 (2H, m), 37-4.0 (2H, m), 2.6-2.8 (2H, m), 13-1.5 (9H, m)

\[856\]
Mass (m/e) 362 (M+1)

\[857\]

\[858\] PREPARATION 29: Synthesis of 4S-fluoro-2S-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester
[859] The title compound was synthesized in the same manner as in PREPARATION 2. Yield 24.1%

[860] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.2-5.5 (2H, m), 37-4.0 (2H, m), 2.9-3.1 (1H, m), 1.2-2.2 (10H, m)

[861] Mass (m/e) 368 (M+1)


[864] The title compound was synthesized in the same manner as in PREPARATION 2. Yield 188%

[865] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.2-5.5 (2H, m), 37-4.0 (2H, m), 27-29 (2H, m), 2.1-23 (2H, m), 13-1.8 (8H, m), 133 (3H, s)

[866] Mass (m/e) 382 (M+1)


[869] The title compound was synthesized in the same manner as in PREPARATION 2. Yield 353%

[870] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.1-5.4 (2H, m), 37-4.0 (2H, m), 2.5-27 (2H, m), 1.58 (3H, m), 13 (2H, m), 0.9 (2H, m)

[871] Mass (m/e) 340 (M+1)


[874] The title compound was synthesized in the same manner as in PREPARATION 2. Yield 36.5%

[875] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 6.9-7.0 (2H, m), 5.2-5.5 (2H, m), 37-4.0 (2H, m), 26-28 (2H, m), 236 (3H, s), 23 (6H, s)

[876] Mass (m/e) 404 (M+1)

[877] PREPARATION 33: Synthesis of 2-bromo-1-[4S-fluoro-2S-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl
[879] 77 mg (0.26 mmol) of 4S-fluoro-2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester was dissolved in 3.4M HCl/EtOH, and the resulting mixture was stirred for about 20 minutes and then distilled off under reduced pressure. The resulting compound, ((4S-fluoro-pyrrolidine-2S,yl)-(5-methyl-[1,3,4]oxadiazole-2-y1)-methanone), was dissolved in about 5 ml of dichloromethane and cooled to 0°C. To this were added dropwise in sequence 25 µl (0.29 mmol) of bromoacetyl bromide and 72 µl (0.52 mmol) of triethylamine, followed by stirring for about 15 minutes. Water was added dropwise to quench the reaction, which was extracted 3 times with dichloromethane. The organic layer was separated, washed once with aqueous NaCl, dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure and then purified by column chromatography (hexane : ethyl acetate = 1 : 2) to give 2.4 mg of the title compound in a yield of 30%.

[880] \[ {^1}^H \text{NMR (CDCl}_3 \] δ 53-5-7 (2H, m), 4.0-4.2 (2H, m), 3.8-4.0 (2H, m), 27-29 (1H, m), 2.6-2.7 (3H, m), 2.2-2.4 (1H, m)

[881] Mass (m/e) 320,322 (M, M+2)

[882]

[883] PREPARATION 34: Synthesis of 2-bromo-1-[4S-fluoro-2S-(5-{1,1-dimethyl-propyl}-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone

[884] The title compound was synthesized in the same manner as in PREPARATION 11. Yield : 37.2%

[885] \[ {^1}^H \text{NMR (CDCl}_3 \] δ 53-5-7 (2H, m), 4.0-4.2 (2H, m), 39 (2H, Abq, J = 15 Hz), 27-2.9 (2H, m), 1.8 (2H, q, J = 7.5 Hz), 1.4-1.5 (6H, m), 0.86 (3H, t, J = 7.5 Hz)

[886] Mass (m/e) 376,378 (M, M+2)

[887]

[888] PREPARATION 35: Synthesis of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone

[889] The title compound was synthesized in the same manner as in PREPARATION 11. Yield : 47.2%

[890] \[ {^1}^H \text{NMR (CDCl}_3 \] δ 53-5.7 (2H, m), 4.0-4.2 (2H, m), 39 (2H, Abq, J = 10 Hz), 2.6-2.8 (2H, m), 1.47 (9H, s)

[891] Mass (m/e) 344, 346 (M, M+2)
PREPARATION 36: Synthesis of 2-bromo-1-[4S-fluoro-2S-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone

The title compound was synthesized in the same manner as in PREPARATION 11. Yield: 67.5%

$^1$H NMR (CDCl$_3$) δ 53.5-5.7 (2H, m), 4.0-4.2 (2H, m), 3.9 (2H, Abq, J = 15 Hz), 2.7-2.9 (2H, m), 1.8 (2H, q, J = 7.5 Hz), 1.4-1.5 (6H, m), 0.86 (3H, t, J = 7.5 Hz)

Mass (m/e) 382, 384 (M, M+2)

PREPARATION 37: Synthesis of 2-bromo-1-[4S-fluoro-2S-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone

The title compound was synthesized in the same manner as in PREPARATION 11. Yield: 41.7%

$^1$H NMR (CDCl$_3$) δ 53.5-5.6 (2H, m), 4.0-4.2 (2H, m), 3.7-4.0 (2H, m), 3.5-3.8, 3.2-3.4 (1H, m), 2.9-3.1 (1H, m), 2.6-2.8 (1H, m), 1.3-2.1 (10H, m)

Mass (m/e) 388, 390 (M, M+2)

PREPARATION 38: Synthesis of 2-bromo-1-[4S-fluoro-2S-(5-(1-methyl-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone

The title compound was synthesized in the same manner as in PREPARATION 11. Yield: 56.9%

$^1$H NMR (CDCl$_3$) δ 5.2-5.6 (2H, m), 4.0-4.2 (2H, m), 3.7-4.0 (2H, m), 2.5-2.8 (2H, m), 2.1-2.3 (2H, m), 1.3-1.8 (11H, m)

Mass (m/e) 402, 404 (M, M+2)

PREPARATION 39: Synthesis of 2-bromo-1-[4S-fluoro-2S-(5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone

The title compound was synthesized in the same manner as in PREPARATION 11. Yield: 75.4%

$^1$H NMR (CDCl$_3$) δ 5.2-5.6 (2H, m), 4.0-4.2 (2H, m), 3.7-4.0 (2H, m), 2.5-2.8 (2H, m), 1.6 (3H, m), 1.4 (2H, m), 1.06 (2H, m)
[911] Mass (m/e) 360, 362 (M, M+2)


The title compound was synthesized in the same manner as in PREPARATION 11. Yield : 42.8%

[915] $^1$H NMR (CDCl$_3$) 7.0 (2H, s), 53-5.7 (2H, m), 4.0-4.2 (2H, m), 37-4.0 (2H, m), 2.6-2.9 (2H, m), 233 (3H, s), 2.29 (6H, s)

[916] Mass (m/e) 424, 426 (M, M+2)

[918] PREPARATION 41: Synthesis of 3-chloro-1-[2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-propane-1-one

The title compound was synthesized in the same manner as in PREPARATION 11. Yield : 70%

[920] $^1$H NMR (CDCl$_3$) $\delta$ 53-5.7 (2H, m), 37-4.1 (4H, m), 2.5-3.0 (4H, m), 1.45 (9H, s)

[921] Mass (m/e) 332 (M+1)


2.0 mg of the title compound was obtained in a yield of 68% in the same manner as in EXAMPLE 1, except that 2.4 mg of 2-bromo-1[4S-fluoro-2S-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 33 and 23 mg of 1-adamantaneamine were reacted.

[925] $^1$H NMR (CDCl$_3$) $\delta$ 53-5.6 (2H,m), 39-4.1 (2H, m), 33-36 (2H,m), 2.6-27 (3H,m), 2.0-23 (5H, m), 1.5-1.8 (12H, m)

[926] Mass (m/e) 391 (M+1)


1.9 mg of the title compound was obtained in a yield of 20% in the same manner as in EXAMPLE 1, except that 9.0 mg of 2-bromo-1-[4S-fluoro-2S-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 33 and 7.6 mg of cumylamine were reacted.
\[ ^1H \text{NMR} (\text{CDCl}_3) \delta 73-7.5 (3H, m), 7.2-7.3 (2H, m), 5.2-5.6 (2H, m), 3.5-3.9 (2H, m), 3.1-3.3 (2H, m), 2.66 (3H, s), 2.0-2.3 (2H, m), 1.2-1.5 (6H, m) \]

Mass (m/e) 375 (M+1)

EXAMPLE 63: Synthesis of 2-tert-butylamino-1-(2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone

7.4 mg of the title compound was obtained in a yield of 50% in the same manner as in EXAMPLE 1, except that 15 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 9.0 \( \mu l \) of tert-butylamine were reacted.

\[ ^1H \text{NMR} (\text{CDCl}_3) \delta 53-5.7 (2H, m), 39-4.1 (2H, m), 33-36 (2H, m), 27-28 (1H, m), 2.05-2.2 (1H, m), 1.49 (9H, m), 0.9-1.2 (9H, m) \]

Mass (m/e) 355 (M+1)

EXAMPLE 64: Synthesis of 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone

11.9 mg of the title compound was obtained in a yield of 64% in the same manner as in EXAMPLE 1, except that 15 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 14 mg of 4-fluoro-phenyl-1,1-dimethyl-ethylamine were reacted.

\[ ^1H \text{NMR} (\text{CDCl}_3) \delta 7.05-7.15 (2H, m), 6.9-7.0 (2H, m), 53-5.7 (2H, m), 39-4.05 (2H, m), 335-36 (2H, m), 26-2.8 (3H, m), 2.15-2.25 (1H, m), 1.47 (9H, m), 0.8-1.1 (6H, m) \]

Mass (m/e) 449 (M+1)

EXAMPLE 65: Synthesis of 2-tert-butylamino-1-[4S-fluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

4.2 mg of the title compound was obtained in a yield of 11% in the same manner as in EXAMPLE 1, except that 40 mg of 2-bromo-1-[4S-fluoro-2S-(5-methyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 33 and 26 \( \mu l \) of tert-butylamine were reacted.

\[ ^1H \text{NMR} (\text{CDCl}_3) \delta 53-5.7 (2H, m), 39-4.1 (2H, m), 33-36 (2H, m), 27-28 (1H, m), 2.67 (3H, m), 2.2-2.4 (1H, m), 0.9-1.2 (9H, m) \]
[946] Mass (m/e) 313 (M+1)

[947]

[948] EXAMPLE 66: Synthesis of 1-[4S-fluoro-2-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone

[949] 4.1 mg of the title compound was obtained in a yield of 80% in the same manner as in EXAMPLE 1, except that 40 mg of 2-bromo-1-[4S-fluoro-2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 33 and 42 mg of 4-fluoro-phenyl-1,1-dimethyl-ethylamine were reacted.

[950] $^1$H NMR (CD3OD) δ 7.05-7.15 (2H, m), 6.9-7.0 (2H, m), 53-5.7 (2H, m), 39-4.05 (2H, m), 335-3.6 (2H, m), 2.6-2.8 (6H, m), 2.15-2.35 (1H, m), 1.0-1.15 (6H, m)

[951] Mass (m/e) 407 (M+1)

[952]


[954] 1.0 mg of the title compound was obtained in a yield of 113% in the same manner as in EXAMPLE 1, except that 7.2 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 8 mg of 2-amino-2-methyl-1-phenyl-propane-1-ol were reacted.

[955] $^1$H NMR (CDCl₃) δ 7.20-7.4 (5H, m), 535-5.6 (2H, m), 43-4.6 (1H, m), 38-4.1 (2H, m), 35-3.7 (2H, m), 349 (2H, s), 27-29 (1H, m), 22-2.4 (1H, m), 1.4-1.6 (9H, m), 0.9-1.1 (6H, m)

[956] Mass (m/e) 447 (M+1)

[957]


[959] 1.0 mg of the title compound was obtained in a yield of 9.6% in the same manner as in EXAMPLE 1, except that 83 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 9 mg of 2-amino-1-cyclohexyl-2-methyl-propane-1-ol were reacted.

[960] $^1$H NMR (CDCl₃) δ 53-5.7 (2H, m), 38-4.0 (2H, m), 30-37 (4H, m), 27-29 (1H, m), 1.2-23 (12H, m), 1.47 (9H, s), 1.0-1.2 (6H, m)

[961] Mass (m/e) 453 (M+1)
EXAMPLE 69: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamino)-ethanone

3.6 mg of the title compound was obtained in a yield of 24% in the same manner as in EXAMPLE 1, except that 14.7 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 10 mg of 1-hydroxymethyl-cyclopropylamine were reacted.

$^1$H NMR (CDCl$_3$) δ 5.1-5.4 (1H, m), 4.5-4.6 (1H, t, J = 8 Hz), 4.2-4.4 (2H, m), 3.93 (1H, d, J = 16 Hz), 3.4-3.6 (2H, m), 2.77 (1H, d, J = 12 Hz), 2.1-2.5 (2H, m), 1.46 (9H, s), 0.03-0.7 (3H, m), 0(2H, m)

EXAMPLE 70: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone

1.8 mg of the title compound was obtained in a yield of 10.5% in the same manner as in EXAMPLE 1, except that 14.2 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 15 mg of 2-cyclohexyl-1,1-dimethyl-ethylamine were reacted.

$^1$H NMR (CDCl$_3$) δ 5.3-5.6 (2H, m), 3.9-4.0 (2H, m), 3.3-3.6 (2H, m), 2.7-2.8 (1H, m), 1.6-1.8 (4H, m), 1.47 (9H, s), 1.0-1.4 (9H, m), 1.05 (3H, s), 1.03 (3H, s)

Mass (m/e) 437 (M+1)

EXAMPLE 71: Synthesis of 2-[2-2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propionic acid tert-butyl ester

10.7 mg of the title compound was obtained in a yield of 24.4% in the same manner as in EXAMPLE 1, except that 36 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 32 mg of 2-amino-2-methyl-propionic acid tert-butyl ester were reacted.

$^1$H NMR (CDCl$_3$) δ 5.3-5.7 (2H, m), 3.8-4.0 (2H, m), 3.3-3.6 (2H, m), 2.6-2.8 (1H, m), 2.1-2.3 (1H, m), 1.47 (9H, s), 1.43 (9H, s), 1.05 (3H, s), 1.2-1.4 (6H, m)
EXAMPLE 72: Synthesis of 2-[2-[(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino]-2-methyl-propionic acid

0.5 ml of trifluoroacetic acid and a catalytic amount of triethylsilane were added dropwise to 6 mg of 2-[(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino]-2-methyl-propionic acid tert-butyl ester synthesized in EXAMPLE 71 in the presence of dichloromethane, and reacted for about 1 hour 30 minutes, concentrated and isolated and purified by Prep-TLC to give 3.2 mg of the title compound in a yield of 60%.

EXAMPLE 73: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentlylamino)-ethanone

3.6 mg of the title compound was obtained in a yield of 32.9% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 84 mg of (1-amino-cyclopentyl)-methanol were reacted.

$^1$H NMR (CDCl$_3$) δ 5.3-5.7 (2H, m), 3.8-4.0 (2H, m), 3.3-3.6 (4H, m), 3.16 (2H, Abq, J = 8 Hz), 2.6-2.8 (1H, m), 2.1-2.3 (1H, m), 1.3-1.7 (8H, m), 1.48 (9H, s)

EXAMPLE 74: Synthesis of 1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

10 mg of the title compound was obtained in a yield of 58.9% in the same manner as in EXAMPLE 1, except that 16 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 9 mg of 2-methoxy-1,1-dimethyl-ethylamine were reacted.

$^1$H NMR (CDCl$_3$) δ 5.2-5.6 (2H, m), 3.9-4.0 (2H, m), 3.1-3.7 (7H, m), 2.6-2.8 (1H, m), 2.1-2.3 (1H, m), 1.46 (9H, s), 1.0-1.1 (6H, m)

Mass (m/e) 385 (M+1)
EXAMPLE 75: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethyl amino)-ethanone

9 mg of the title compound was obtained in a yield of 49.2% in the same manner as in EXAMPLE 1, except that 16 mg of 2-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 12 mg of 2-methoxymethoxy-1,1-dimethyl-ethylamine were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 5.2-5.6 (2H, m), 4.5-4.7 (2H, m), 3.9-4.0 (2H, m), 33-36 (7H, m), 2.6-2.8 (1H, m), 2.1-2.3 (1H, m), 1.46 (9H, s), 1.0-1.1 (6H, m)

Mass (m/e) 415 (M+1)

EXAMPLE 76: Synthesis of 2-tert-butylamino-1-[4S-fluoro-2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

6.7 mg of the title compound was obtained in a yield of 22.8% in the same manner as in EXAMPLE 1, except that 30 mg of 2-bromo-1-[4S-fluoro-2S-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 36 and 11.5 mg of tert-butylamine were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 81-82 (2H, m), 7.5-7.7 (3H, m), 5.2-5.7 (2H, m), 39-4.1 (2H, m), 33-36 (2H, m), 27-2.8 (1H, m), 22-2.4 (1H, m), 1.0-1.2 (9H, m)

Mass (m/e) 375 (M+1)

EXAMPLE 77: Synthesis of 1-[4S-fluoro-2-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

13 mg of the title compound was obtained in a yield of 4.2% in the same manner as in EXAMPLE 1, except that 30 mg of 2-bromo-1-[4S-fluoro-2S-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 36 and 14 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 81-82 (2H, m), 7.5-7.7 (3H, m), 53-5.7 (2H, m), 39-4.1 (2H, m), 331-36 (4H, m), 27-2.9 (1H, m), 22-2.4 (1H, m), 1.0-1.1 (6H, m)

Mass (m/e) 391 (M+1)

EXAMPLE 78: Synthesis of 1-[4S-fluoro-2-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

12.4 mg of the title compound was obtained in a yield of 39.1% in the same manner as in EXAMPLE 1, except that 30 mg of
2-bromo-1-[4S-fluoro-2S-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 36 and 16.2 mg of 2-methoxy-1,1-dimethyl-ethylamine were reacted.

**[1008]** $^1$H NMR (CDCl$_3$) $\delta$ 8.1-8.2 (2H, m), 7.5-7.7 (3H, m), 5.2-5.8 (2H, m), 3.9-4.1 (2H, m), 3.5-3.6 (1H, m), 3.3-3.4 (3H, m), 3.1-3.2 (2H, m), 2.6-2.7 (1H, m), 2.2-2.4 (1H, m), 1.0-1.1 (6H, m)

**[1009]** Mass (m/e) 405 (M+1)

**[1010]**

**EXAMPLE 79: Synthesis of 1-[4S-fluoro-2-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone**

**[1011]** 7.8 mg of the title compound was obtained in a yield of 22.9% in the same manner as in EXAMPLE 1, except that 30 mg of 2-bromo-1-[4S-fluoro-2S-(5-phenyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 36 and 21 mg of 2-methoxymethoxy-1,1-dimethyl-ethylamine were reacted.

**[1012]** $^1$H NMR (CDCl$_3$) $\delta$ 8.1-8.2 (2H, m), 7.5-7.7 (3H, m), 5.2-5.8 (2H, m), 4.5-4.7 (2H, m), 3.9-4.1 (2H, m), 3.5-3.6 (1H, m), 3.3-3.4 (5H, m), 2.6-2.7 (1H, m), 2.2-2.4 (1H, m), 1.0-1.1 (6H, m)

**[1013]** Mass (m/e) 435 (M+1)

**[1014]**

**EXAMPLE 80: Synthesis of 2-tert-butyldioxime-1-[2-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone**

**[1015]** 39 mg of the title compound was obtained in a yield of 39.8% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[4S-fluoro-2S-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 37 and 3.8 mg of tert-butyldioxime were reacted.

**[1016]** $^1$H NMR (CDCl$_3$) $\delta$ 5.2-5.7 (2H, m), 3.8-4.1 (2H, m), 3.4-3.6 (2H, m), 2.9-3.0 (1H, m), 2.6-2.8 (1H, m), 2.2-2.4 (1H, m), 1.2-2.1 (10H, m), 1.0-1.2 (9H, m)

**[1017]** Mass (m/e) 381 (M+1)

**[1018]**

**EXAMPLE 81: Synthesis of 1-[2-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone**

**[1019]** 39 mg of the title compound was obtained in a yield of 19.1% in the same manner
as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[4S-fluoro-2S-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 37 and 9.2 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

\[1023\]

\[\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3})} \delta 5.2-5.7 (2H, m), 38.4-1.1 (2H, m), 30-36 (4H, m), 29-30 (1H, m), 26-2.8 (1H, m), 22-24 (1H, m), 1.2-21 (10H, m), 1.0-1.2 (6H, m)\]

\[1024\]

Mass (m/e) 397 (M+1)

\[1025\]

\[1026\] EXAMPLE 82: Synthesis of 1-[2-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

\[1027\]

8.2 mg of the title compound was obtained in a yield of 38.3% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[4S-fluoro-2S-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 37 and 10.6 mg of 2-methoxy-1,1-dimethyl-ethylamine were reacted.

\[1028\]

\[\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3})} \delta 5.2-5.7 (2H, m), 38.4-1.1 (2H, m), 30-36 (7H, m), 29-30 (1H, m), 26-2.8 (1H, m), 22-24 (1H, m), 1.2-21 (10H, m), 1.0-1.2 (6H, m)\]

\[1029\]

Mass (m/e) 411 (M+1)

\[1030\]

\[1031\] EXAMPLE 83: Synthesis of 1-[2-(5-cyclohexyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

\[1032\]

6.5 mg of the title compound was obtained in a yield of 28.6% in the same manner as in EXAMPLE 1, except that 20 mg of 2-bromo-1-[4S-fluoro-2S-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 37 and 1372 mg of 2-methoxymethoxy-1,1-dimethyl-ethylamine were reacted.

\[1033\]

\[\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3})} \delta 5.2-5.7 (2H, m), 4.5-4.7 (2H, m), 38-4.1 (2H, m), 30-36 (7H, m), 29-30 (1H, m), 26-2.8 (1H, m), 22-24 (1H, m), 1.2-21 (10H, m), 1.0-1.2 (6H, m)\]

\[1034\]

Mass (m/e) 441 (M+1)

\[1035\]

\[1036\] EXAMPLE 84: Synthesis of 2-tert-butyramino-1-[4S-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carb
onyl]-pyrrolidine-1-yl]-ethanone

[1037] 13 mg of the title compound was obtained in a yield of 133% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[4S-fluoro-2S-(5-(1-methyl-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 38 and 3.6 mg of tert-butylamine were reacted.

[1038] $^1$H NMR (CDCl$_3$) δ 5.2-5.7 (2H, m), 39-4.1 (2H, m), 33-36 (2H, m), 345 (2H, Abq, J = 16 Hz), 26-2.8 (1H, m), 22-23 (3H, m), 20-2.15 (3H, m), 13-1.7 (8H, m), 1.37 (3H, s), 0.9-1.1 (9H, m)

[1039] Mass (m/e) 395 (M+1)

[1040]


[1042] 1.2 mg of the title compound was obtained in a yield of 11.8% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[4S-fluoro-2S-(5-(1-methyl-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 38 and 4.4 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

[1043] $^1$H NMR (CDCl$_3$) δ 53-5.7 (2H, m), 38-4.1 (2H, m), 33-37 (3H, m), 3.12 (1H, Abq, J = 12 Hz), 27-2.8 (1H, m), 22-23 (3H, m), 20-2.15 (3H, m), 13-1.7 (8H, m), 1.37 (3H, s), 1.0-1.2 (6H, m)

[1044] Mass (m/e) 411 (M+1)

[1045]

[1046] EXAMPLE 86: Synthesis of 2-tert-butylamino-1-[2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-ethanone

[1047] 2.9 mg of the title compound was obtained in a yield of 29.6% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[4S-fluoro-2S-(5-[1,1-dimethyl-propyl]-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 34 and 3.9 mg of tert-butylamine were reacted.

[1048] $^1$H NMR (CDCl$_3$) δ 5.2-5.7 (2H, m), 39-4.1 (2H, m), 33-36 (2H, m), 26-2.8 (1H, m), 2.1-23 (1H, m), 1.79 (2H, q, J = 7.5 Hz), 1.43 (6H, s), 1.0-1.2 (9H, m), 0.84 (3H, t, J = 7.5 Hz)
[1049] Mass (m/e) 369 (M+1)

[1050]

[1051] **EXAMPLE 87**: Synthesis of 1-[2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[1052] 1.0mg of the title compound was obtained in a yield of 9.8% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[4S-fluoro-2S-(5-[1,1-dimethyl-propyl]-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 34 and 4.7 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

[1053] \(^1\)H NMR (CDCl\textsubscript{3}) \(\delta 5.2-5.7\) (2H, m), 3.8-4.1 (2H, m), 3.0-3.6 (4H, m), 27-28 (1H, m), 2.1-23 (1H, m), 1.80 (2H, q, J = 7.0 Hz), 1.43 (6H, s), 1.0-1.2 (6H, m), 0.85 (3H, t, J = 7.0 Hz)

[1054] Mass (m/e) 385 (M+1)

[1055]

[1056] **EXAMPLE 88**: Synthesis of 1-[2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[1057] 1.7 mg of the title compound was obtained in a yield of 15.6% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[4S-fluoro-2S-(5-[1,1-dimethyl-propyl]-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 34 and 6 mg of 1-hydroxy-cyclopentylamine were reacted.

[1058] \(^1\)H NMR (CDCl\textsubscript{3}) \(\delta 5.3\) (1H, d, J = 50 Hz), 4.42 (1H, m), 4.1 (2H, Abq, J = 17.5 Hz), 3.6-39 (4H, m), 2.65 (2H, td, J = 9.5, 6.5 Hz), 2.1-23 (3H, m), 1.5-1.9 (7H, m), 13-1.5 (6H, m), 0.82 (3H, t, J = 80 Hz)

[1059] Mass (m/e) 411 (M+1)

[1060]

[1061] **EXAMPLE 89**: Synthesis of 2-tert-butyl-1-[4S-fluoro-2-[5-(1-methyl-cyclopropyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

[1062] 37 mg of the title compound was obtained in a yield of 37.8% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[4S-fluoro-2S-(5-(1-methyl-cyclopropyl)-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 39 and 4.1 mg of tert-butylamine
were reacted.

$^1$H NMR (CDCl$_3$) δ 5.2-5.7 (2H, m), 3.9-4.1 (2H, m), 3.3-3.6 (2H, m), 2.6-2.8 (1H, m), 2.1-2.3 (1H, m), 1.55-1.65 (3H, m), 1.42 (2H, m), 1.0-1.2 (9H, m), 1.03 (2H, m)

Mass (m/e) 353 (M+1)

EXAMPLE 90: Synthesis of
1-{4S-fluoro-2-[5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine
-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

1.6 mg of the title compound was obtained in a yield of 15.6% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-{4S-fluoro-2S-(5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 39 and 4.9 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

$^1$H NMR (CDCl$_3$) δ 5.2-5.7 (2H, m), 3.8-4.1 (2H, m), 3.0-3.6 (4H, m), 2.6-2.8 (1H, m), 2.1-2.3 (1H, m), 1.55-1.65 (3H, m), 1.44 (2H, m), 1.0-1.2 (8H, m)

Mass (m/e) 369 (M+1)

EXAMPLE 91: Synthesis of
1-{4S-fluoro-2-[5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine
-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

5.0 mg of the title compound was obtained in a yield of 45.7% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-{4S-fluoro-2S-(5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1]-ethanone synthesized in PREPARATION 39 and 6.4 mg of 1-hydroxymethyl-cyclopentylamine were reacted.

$^1$H NMR (CDCl$_3$) δ 5.2-5.7 (2H, m), 3.6-4.2 (3H, m), 3.0-3.6 (3H, m), 2.6-2.8 (1H, m), 2.1-2.3 (1H, m), 1.4-1.9 (10H, m), 1.60 (3H, s), 1.05 (2H, m)

Mass (m/e) 395 (M+1)

EXAMPLE 92: Synthesis of
2-tert-butyl-1-{4S-fluoro-2-[5-(2,4,6-trimethyl-phenyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone

39 mg of the title compound was obtained in a yield of 39.7% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-{4S-fluoro-2S-(5-(2,4,6-trimethyl-phenyl-[1,3,4]oxadiazole-2-carbonyl)-p
yrrolidine-1)-ethanone synthesized in PREPARATION 40 and 34 mg of tert-butylamine were reacted.

[1078] $^1$H NMR (CDCl$_3$) δ 6.97 (2H, s), 5.2-5.7 (2H, m), 39-4.1 (2H, m), 34-3.6 (2H, m), 27-2.9 (1H, m), 233 (3H, s), 230 (6H, s), 20-2.2 (1H, m), 1.0-1.2 (9H, m)

[1079] Mass (m/e) 417 (M+1)

[1080]


[1082] 46 mg of the title compound was obtained in a yield of 93.4% in the same manner as in EXAMPLE 1, except that 50 mg of 2-bromo-1-(2S)-(5-tert-butyl-1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 33 μl of (2-hydroxy-ethyl)-methyl-amine were reacted.

[1083] $^1$H NMR (CDCl$_3$) δ 5.2-5.8 (2H, m), 38-43 (2H, m), 31-37(4H, m), 2.6-2.8(3H, m), 2.1-2.5 (4H, m), 1.48 (9H, m)

[1084] Mass (m/e) 357 (M+1)

[1085]

[1086] **EXAMPLE 94: Synthesis of 1-[2-[5-tert-butyl-1,3,4] oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-3-(2-hydroxy-1,1-dimethyl-ethylamino)-propene-1-one**

[1087] 281 mg of the title compound was obtained in a yield of 84.3% in the same manner as in EXAMPLE 1, except that 30 mg of 3-chloro-1-[2S-(5-tert-butyl-1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-propene-1-one synthesized in PREPARATION 41 and 29 μl of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

[1088] $^1$H NMR (CDCl$_3$) δ 5.2-5.6 (2H, m), 39-4.1 (2H, m), 32-3.5 (2H, m), 2.8-3.0 (3H, m), 2.4-2.5 (2H, m), 2.1-2.3 (1H, m), 1.47 (9H, s), 1.0-1.1 (6H, m)

[1089] Mass (m/e) 385 (M+1)

[1090]

[1091] **EXAMPLE 95: Synthesis of 1-[2-[5-tert-butyl-1,3,4] oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-3-[2-hydroxy-ethyl]-methyl-amino]-propene-1-one**

[1092] 15.0 mg of the title compound was obtained in a yield of 42.9% in the same manner as in EXAMPLE 1, except that 30 mg of 3-chloro-1-[2S-(5-tert-butyl-1,3,4] oxadiazole-2-carbonyl)-4-fluoro-pyrrolidine-1-yl]-propene-1-one synthesized in PREPARATION 41 and 22 μl of (2-hydroxy-ethyl)-methyl-amine were reacted.
1H NMR (CDCl₃) δ 5.2-5.6 (2H, m), 3.9-4.1 (2H, m), 3.5-37 (2H, m), 2.9 (1H, m), 2.72 (2H, t, J = 7 Hz), 2.45-2.6 (2H, m), 2.46 (2H, t, J = 7 Hz), 2.1-23 (4H, m), 1.45 (9H, s)

Mass (m/e) 371 (M+1)

EXAMPLE 96: Synthesis of 1-[2-[5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-3-(2-hydroxymethyl-piperidine-1-yl)-propane-1-one

21.8 mg of the title compound was obtained in a yield of 587% in the same manner as in EXAMPLE 1, except that 30 mg of 3-chloro-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4-fluoro-pyrrolidine-1-yl]-propane-1-one synthesized in PREPARATION 41 and 31 mg of 2-hydroxymethyl-piperidine were reacted.

1H NMR (CDCl₃) δ 5.2-5.7 (2H, m), 3.9-4.1 (2H, m), 3.7-3.85 (1H, m), 3.3-3.5 (1H, m), 3.1-3.3 (1H, m), 2.9-31 (1H, m), 2.1-28 (5H, m), 1.2-1.8 (6H, m), 1.45 (9H, s)

Mass (m/e) 411 (M+1)

EXAMPLE 97: Synthesis of 6-(2-[2-[5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide

5 mg of the title compound was obtained in a yield of 327% in the same manner as in EXAMPLE 1, except that 10 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 23 mg of 6-(2-amino-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide synthesized by a method as disclosed in WO 02/051836 were reacted.

1H NMR (CDCl₃) δ 8.42 (1H, m), 7.63 (1H, m), 6.43 (1H, m), 5.8-6.0 (1H, m), 5.3-5.6 (2H, m), 3.8-4.0 (2H, m), 3.1-3.6 (4H, m), 2.6-2.8 (1H, m), 2.68 (6H, s), 2.1-23 (1H, m), 1.4-1.5 (9H, m), 1.0-1.2 (6H, m)

Mass (m/e) 554 (M+1)

EXAMPLE 98: Synthesis of 6-(2-[3-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-3-oxo-ethylamino)-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide

2.4 mg of the title compound was obtained in a yield of 14.0% in the same manner as in EXAMPLE 1, except that 10 mg of 3-chloro-1-[2S-(5-tert-butyl-[1,3,4]
oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-propane-1-one synthesized in PREPARATION 41 and 25 mg of 6-(2-amino-2-methyl-propylamino)-pyridine-3-sulfinic acid dimethylamide synthesized by a method as disclosed in WO 02/051836 were reacted.

[1108] $^1$H NMR (CDCl$_3$) $\delta$ 8.40 (1H, br s), 7.6 (1H, m), 63-6.5 (2H, m), 53-5.6 (2H, m), 39-4.1 (2H, m), 33-3.5 (2H, m), 2.8-3.0 (2H, m), 2.67 (6H, s), 2.5-2.8 (3H, m), 2.1-2.3 (1H, m), 1.4-1.5 (9H, m), 1.0-1.2 (6H, m)

[1109] Mass (m/e) 568 (M+1)

[1110]


[1112] 37 mg of the title compound was obtained in a yield of 37% in the same manner as in EXAMPLE 1, except that 80 mg (0.022 mmol) of 2-bromo-1-[(2S)-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 11.0 mg (0.066 mmol) of 1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamine synthesized by a method as disclosed in WO 02/051836 were reacted.

[1113] $^1$H NMR (CDCl$_3$) $\delta$ 8.06-8.03 (m, 1H), 7.40-7.34 (m, 1H), 6.55-6.50 (m, 1H), 6.46-6.41 (m, 1H), 5.49-5.16 (m, 3H), 4.02-3.81 (m, 2H), 3.57-3.13 (m, 4H), 2.80-2.48 (m, 1H), 2.30-2.14 (m, 1H), 2.06-1.70 (m, 7H), 1.47-1.40 (m, 9H), 1.31-1.08 (m, 8H).

[1114] Mass (m/e) 447 (M+1)

[1115]

[1116] EXAMPLE 100: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl]-ethanone

[1117] 113 mg of the title compound was obtained in a yield of 85% in the same manner as in EXAMPLE 1, except that 10.0 mg (0.028 mmol) of 2-bromo-1-[(2S)-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 15.9 mg (0.083 mmol) of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine synthesized by a method as disclosed in WO 03/004498 were reacted.

[1118] $^1$H NMR (CDCl$_3$) $\delta$ 5.68-5.25 (m, 2H), 4.32-377 (m, 7H), 3.69-3.48 (m, 2H), 3.36-3.33 (m, 1H), 3.19-3.08 (m, 1H), 2.93-2.59 (m, 2H), 1.51-1.41 (m, 9H).

[1119] Mass (m/e) 474 (M+1)
EXAMPLE 101: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(1-benzyl-4-methyl-piperidine-4-ylamino)-ethanone

6.8 mg of the title compound was obtained in a yield of 74% in the same manner as in EXAMPLE 1, except that 6.8 mg (0.019 mmol) of 2-bromo-1-[(2S)-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 11.5 mg (0.058 mmol) of 1-benzyl-4-methyl-piperidine-4-ylamine synthesized by a method as disclosed in EP 0647639 A1 were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 731-7.21 (m, 5H), 5.64-5.28 (m, 2H), 4.03-3.84 (m, 2H), 3.51-3.29 (m, 4H), 279-2.68 (m, 1H), 2.44-2.15 (m, 4H), 1.68-1.41 (m, 17H), 1.09-1.03 (m, 3H).

Mass (m/e) 486 (M+1)

EXAMPLE 102: Synthesis of 1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(4-methyl-1-piperidine-4-yl-piperidine-4-ylamino)-ethanone

82 mg of the title compound was obtained in a yield of 63% in the same manner as in EXAMPLE 1, except that 10.0 mg (0.028 mmol) of 2-bromo-1-[(2S)-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 19.0 mg (0.083 mmol) of 4-methyl-1-pyrimidine-2-yl-piperidine-4-ylamine synthesized by a method as disclosed in WO 02/051836 were reacted.

$^1$H NMR (CDCl$_3$) $\delta$ 829-2.26 (m, 2H), 6.45-6.42 (m, 1H), 5.64-5.30 (m, 2H), 4.06-374 (m, 5H), 3.53-334 (m, 2H), 278-2.55 (m, 2H), 231-2.17 (m, 1H), 1.64-1.45 (m, 20H), 1.30-1.26 (m, 1H), 1.17-1.10 (m, 3H).

Mass (m/e) 474 (M+1)

EXAMPLE 103: Synthesis of 1-(4-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino)-4-methyl-piperidine-1-yl]-2-hydroxy-ethanone

2.4 mg of the title compound was obtained in a yield of 19% in the same manner as in EXAMPLE 1, except that 10.0 mg (0.028 mmol) of 2-bromo-1-[(2S)-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-hydroxy-ethanone.
1\)-ethanone synthesized in PREPARATION 35, and 177 mg (0.085 mmol) of 1-(4-amino-4-methyl-piperidine-1-yi)-2-hydroxy-ethanone synthesized by a method as disclosed in WO 04/09544, and 120 mg (0.085 mmol) of calcium carbonate were reacted.

\[ ^1H \text{NMR (CDCl}_3 ) \delta 5.64-5.30 (m, 2H), 8.14 (d, 2H, J=5.2 Hz), 4.05-3.66 (m, 4H), 3.53-3.28 (m, 4H), 3.18-3.15 (m, 1H), 2.82-2.57 (m, 1H), 2.31-2.14 (m, 1H), 1.65-1.42 (m, 13H), 1.27-1.22 (m, 1H), 1.14-1.05 (m, 3H). \]

Mass (m/e) 454 (M+1)

PREPARATION 42: Synthesis of 4,4-difluoro-2S-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

0.22 g (0.88 mmol) of 4,4-difluoro-pyrrolidine-1,2S-dicarboxylic acid 1-tert-butyl ester and 86 mg (0.88 mmol) of methoxymethylamine were dissolved in dimethylformamide. To the solution, 0.218 g (1.14 mmol) of 1-[3-(dimethylamino)propyl] -3-ethylcarbo-di-imide hydrochloride (EDC) and 0.154 g (1.14 mmol) of 1-hydroxybenzotriazole hydrate (HOBT) was added, and 0.49 ml (332 mmol) of triethylamine was added dropwise, and the resulting mixture was stirred for 15 hours. The reaction was diluted with excess ethyl acetate, and the product was washed once with aqueous HCl and aqueous NaCl, respectively, and dried over anhydrous magnesium sulfate, then filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 2) to give 0.230 g of the title compound in a yield of 89%.

\[ ^1H \text{NMR (CDCl}_3 ) \delta 4.7-4.9 (1H, m), 3.7-4.0 (2H, m), 3.7-3.8 (3H, m), 3.21 (3H, s), 2.6-2.8 (1H, m), 2.2-2.3 (1H, m), 1.4-1.5 (9H, m) \]

Mass (m/e) 277 (M+1)

PREPARATION 43: Synthesis of 4,4-difluoro-2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

0.183 g (2.18 mmol) of 2-methyl-1,3,4-oxadiazole was dissolved in tetrahydrofuran, and the temperature of a reactor was cooled to -78°C. To this was slowly added dropwise 0.87 ml of butyllithium (2.5M in hexane), followed by stirring for 40 minutes. To this was again added 0.561 g (2.54 mmol) of magnesium bromide ethylether complex, followed by stirring for 40 minutes at the same temperature. 0.213 g (0.72 mmol) of
4,4-difluoro-2S-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester, obtained in PREPARATION 10, which was been dissolved in tetrahydrofuran, slowly was added dropwise thereto. Thereafter, the temperature was raised to room temperature. After stirring for about 3 hours, the product was diluted with ethyl acetate, and washed once with aqueous saturated ammonium chloride and aqueous NaCl, respectively, then dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate = 1:1) to give 120 mg of the title compound in a yield of 52%.

[1143] $^1$HNMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 3.8-4.0 (2H, m), 2.8-3.0 (1H, m), 2.6-2.7 (3H, m), 2.5-2.6 (1H, m), 1.4-1.5 (9H, m)

[1144] Mass (m/e) 318 (M+1)

[1145]

[1146] PREPARATION 44: Synthesis of 2-bromo-1-[4,4-difluoro-2S-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

[1147] 120 mg (038 mmol) of 4,4-difluoro-2S-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester obtained in PREPARATION 43 was dissolved in 34M HCl/EA, and the mixture was stirred for about 20 minutes and distilled off under reduced pressure. The resulting compound, ((4,4-difluoro-pyrrolidine-2S-yl)-(5-methyl-[1,3,4]oxadiazole-2-yl)-methanone), was dissolved in about 5 ml of dichloromethane and cooled to 0°C. To this were added 58 µl (0.66 mmol) of bromoacetyl bromide and 170 µl (1.2 mmol) of triethyl amine dropwise in sequence, followed by stirring for about 30 minutes. Water was added dropwise to quench the reaction, which was then extracted 3 times with dichloromethane. The extracted organic layer was separated, washed once with aqueous NaCl, dried over anhydrous magnesium sulfate, and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate = 1:2) to give 60 mg of title compound in a yield of 47%.

[1148] $^1$HNMR (CDCl$_3$) $\delta$ 5.4-5.5 (1H, m), 4.0-4.2 (2H, m), 3.8-4.0 (2H, m), 27-29 (1H, m), 2.6-2.7 (3H, m), 2.5-2.6 (1H, m)

[1149] Mass (m/e) 338,340 (M, M+2)

[1150]

[1151] EXAMPLE 104: Synthesis of
2-(adamantane-1-ylamino)-1-[4,4-difluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

1.7 mg of the title compound was obtained in a yield of 23% in the same manner as in EXAMPLE 1, except that 60 mg of 2-bromo-1-[4,4-difluoro-2S-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 44 and 54 mg of 1-adamantaneamine were reacted.

$^1$H NMR (CDCl$_3$) δ 5.5-5.6 (1H, t, J=8Hz), 4.0-4.2 (2H, m), 3.4-3.6 (2H,m), 2.65 (3H,m), 2.0-2.3 (5H, m), 1.5-1.8 (12H, m)

Mass (m/e) 409 (M+1)

PREPARATION 45: Synthesis of 4R-(methoxy-methyl-carbamoyl)-thiazolidine-3-carboxylic acid tert-butyl ester

10.0 g (42.8 mmol) of thiazolidine-3,4R-dicarboxylic acid 3-tert-butyl ester and 4.2 g (42.8 mmol) of methoxymethylamine were dissolved in dimethylformamide. To the solution, 10.7 g (55.7 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbo-di-imide hydrochloride (EDC) and 7.5 g (55.7 mmol) of 1-hydroxybenzotriazole hydrate (HOBT) were added, and 23.9 ml (171 mmol) of triethylamine was again added dropwise, followed by stirring for 32 hours. The reaction was diluted with excess ethyl acetate, and the product was washed once with aqueous HCl and aqueous NaCl, respectively, dried over anhydrous magnesium sulfate, and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 2) to give 7.0 g of title compound in a yield of 59%.

$^1$H NMR (CDCl$_3$) δ 4.9-5.2 (1H, m), 4.7-4.8 (1H, m), 4.5-4.6 (1H, m), 3.7-3.9 (3H, m), 3.4-3.5 (1H, m), 3.25 (3H, s), 3.0-3.2 (1H, m), 1.4-1.6 (9H, m)

Mass (m/e) 277 (M+1)

PREPARATION 46: Synthesis of 4R-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-thiazolidine-3-carboxylic acid tert-butyl ester

0.40 g (3.17 mmol) of 2-tert-butyl-1,3,4-oxadiazole was dissolved in tetrahydrofuran, and the temperature of a reactor was cooled to -78°C. To this was slowly added dropwise 13 ml of butyllithium (2.5M in hexane), followed by stirring for 40 minutes. To this was added 0.82 g (3.17 mmol) of magnesium bromide ethylether complex, followed by stirring for 40 minutes at the same temperature. 0.29
g (1.06 mmol) of 4R-(methoxy-methylcarbamoyl)-thiazolidine-3-carboxylic acid tert-butyl ester, obtained in PREPARATION 13, which was dissolved in tetrahydrofuran, was added to the resulting solution. Thereafter, the temperature was gradually raised to room temperature. After stirring for about 3 hours, the product was diluted with ethyl acetate, washed once with aqueous saturated ammonium chloride and aqueous NaCl, respectively, and dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 1) to give 265 mg of the title compound in a yield of 74%.

\[ ^1H \text{ NMR (CDCl}_3 \] \( \delta \) 5.5-5.7 (1H, m), 4.6-4.8 (2H, m), 3.55-3.65 (1H, m), 33-34 (1H, m), 13-1.6 (18H, m)

Mass (m/e) 342 (M+1)

PREPARATION 47: Synthesis of 2-bromo-1-[4R-(5-tert-butyl-1,3,4 oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanone

265 mg (0.78 mmol) of 4R-(5-tert-butyl-1,3,4 oxadiazole-2-carbonyl)-thiazolidine-3-carboxylic acid tert-butyl ester obtained in PREPARATION 46 was dissolved in 34M HCl/EA, which was then stirred for about 20 minutes and distilled off under reduced pressure. The resulting compound, (5-tert-butyl-1,3,4 oxadiazole-2-yl)-thiazolidine-4R-yl-methanone), was dissolved in about 5 ml of dichloromethane and cooled to 0°C. To this were added dropwise 74 µl (0.86 mmol) of bromoacetyl bromide and 220 µl (1.56 mmol) of triethyl amine in sequence, followed by stirring for about 30 minutes. Water was added dropwise to quench the reaction, which was then extracted 3 times with dichloromethane. The extracted organic layer was separated, washed once with aqueous NaCl, dried over anhydrous magnesium sulfate, and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 2) to give 134 mg of the title compound in a yield of 48% (two steps).

\[ ^1H \text{ NMR (CDCl}_3 \] \( \delta \) 5.8 (1H, m), 4.83 (2H, s), 38-4.0 (2H, ABq, J=10Hz), 3.59 (1H, dd, J=12.5, 7.5Hz), 335 (1H, dd, J=12.5, 7.5Hz), 1.48 (9H, s)

Mass (m/e) 362,364 (M, M+2)

PREPARATION 48: Synthesis of 2-bromo-1-[4R-(5-methyl-1,3,4 oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanone
Yield: 53%  
$^1$H NMR (CDCl$_3$) $\delta$ 5.7-5.8 (1H, m), 4.83 (2H, s), 3.8-4.0 (2H, ABq, J=10 Hz), 3.56 (1H, dd, J=10, 5.0 Hz), 3.35 (1H, dd, J=10, 5Hz), 2.68(3H, s), 1.48 (9H, s)  
Mass (m/e) 320, 322 (M, M+2)  

**EXAMPLE 105: Synthesis of**  
2-(adamantane-1-ylamino)-1-[4R-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanone  

4.5 mg of the title compound was obtained in a yield of 4.5% in the same manner as in EXAMPLE 1, except that 90 mg of 2-bromo-1-[4R-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanone synthesized in PREPARATION 48 and 85 mg of 1-adamantaneamine were reacted.  
$^1$H NMR (CDCl$_3$) $\delta$ 5.7-5.8 (1H,m), 4.75 (2H, s), 3.55(2H,m), 3.45-3.55 (1H,m), 33 (1H, m), 2.67 (3H, s), 2.0-23 (3H, m), 1.5-1.8 (12H, m)  
Mass (m/e) 391 (M+1)  

**EXAMPLE 106: Synthesis of**  
2-(3-hydroxy-adamantane-1-ylamino)-1-[4R-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanone  

5.0 mg of the title compound was obtained in a yield of 4.0% in the same manner as in EXAMPLE 1, except that 90 mg of 2-bromo-1-[4R-(5-methyl-[1,3,4] oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanone synthesized in PREPARATION 48 and 94 mg of 3-hydroxy-1-adamantane were reacted.  
$^1$H NMR (CDCl$_3$) $\delta$ 5.7-5.8 (1H,m), 4.75 (2H, Abq, J = 8Hz), 3.58 (2H,m), 3.45-3.55 (1H,m), 33-34 (1H, m), 270 (3H, s), 2.0-23 (2H, m), 1.5-1.8 (12H, m)  
Mass (m/e) 407 (M+1)  

**EXAMPLE 107: Synthesis of**  
1-[4R-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-thiazolidine-3-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone  

1.5 mg of the title compound was obtained in a yield of 7.0% in the same manner as in EXAMPLE 1, except that 18 mg of 2-bromo-1-[4R-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanone synthesized in PREPARATION 47 and 17 mg of 4-fluoro-phenyl-1,1-dimethyl-ethylamine were reacted.  
$^1$H NMR (CDCl$_3$) $\delta$ 7.10-7.15 (2H, m), 6.98-7.0 (2H, m), 5.8 (1H,m), 4.7-4.8 (2H,
m), 39-4.0(2H, m), 3.5-37 (3H, m), 33-34 (1H, m), 1.48 (9H, s), 1.26 (3H, s), 1.08
(3H, s)

[1189]  Mass (m/e) 449 (M+1)
[1190]
[1191]  EXAMPLE 108: Synthesis of 1-[4-(5-tert-butyl-[1,3,4]oxadiazole-
2-carbonyl)-thiazolidine-3-yl]-2-[2-methoxy-1,1-dimethyl-ethylamino]-ethanone
[1192]  5 mg of the title compound was obtained in a yield of 9.4% in the same manner as
in EXAMPLE 1, except that 50 mg of 2-bromo-1-[4R-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-thiazolidine-3-yl]-ethanone synthesized in PREPARATION 47 and 28 mg
of 2-methoxy-1,1-dimethyl-ethylamine were reacted.
[1193]  ′H NMR (CDCl₃) δ 5.7-5.8 (1H, m), 4.74 (2H, s), 3.56(2H, Abq, J = 15 Hz), 332
(3H, s), 3.19 (2H, s), 1.45(9H, s), 1.08 (3H, s), 1.07 (3H, s)
[1194]  Mass (m/e) 385 (M+1)
[1195]
[1196]  EXAMPLE 109: Synthesis of 1-[4-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-thiazolidine-3-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-et
hanone
[1197]  7 mg of the title compound was obtained in a yield of 12.2% in the same manner as
in EXAMPLE 1, except that 50 mg of 2-bromo-1-[4R-(5-tert-butyl-[1,3,4] oxadiazole-
2-carbonyl)-thiazolidine-3-yl]-ethanone synthesized in PREPARATION 47 and 37 mg
of 2-methoxymethoxy-1,1-dimethyl-ethylamine were reacted.
[1198]  ′H NMR (CDCl₃) δ 5.7-5.8 (1H, m), 4.74 (2H, s), 4.61 (2H, s), 3.5-36(2H, m),
3.42 (3H, s), 33-34(2H, m), 1.45(9H, s), 1.09 (6H, s)
[1199]  Mass (m/e) 415 (M+1)
[1200]
[1201]  PREPARATION 49: Synthesis of
2R-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl
ester
[1202]  9.34 g (43 mmol) of pyrrolidine-1,2R-dicarboxylic acid 1-tert-butyl ester and 4.23
g (43 mmol) of methoxymethylamine were dissolved in dimethylformamide. To this
were added 10.8 g (56 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbo-di-imide
hydrochloride (EDC) and 7.6 g (56 mmol) of 1-hydroxybenzotriazole hydrate
(HOBT), followed by dropwise addition of 24 ml (173 mmol) of triethylamine and
stirring for 21 hours. The reaction was diluted with excess ethyl acetate, and the
product was washed once with aqueous HCl and aqueous NaCl, respectively, dried
over anhydrous magnesium sulfate, and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 2) to give 93 g of title compound in a yield of 83%.

1H NMR (CDCl₃) δ 4.6-4.8 (1H, m), 3.7-3.8 (3H, m), 3.4-3.7 (2H, m), 3.22 (3H, s), 2.1-2.3 (1H, m), 1.8-2.1 (3H, m), 1.4-1.5 (9H, m)

Mass (m/e) 259 (M+1)

PREPARATION 50: Synthesis of 2R-(5-tert-butyl-[1,3,4] oxadiazole-2R-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

13 g (103 mmol) of 2-tert-butyl-1,3,4-oxadiazole was dissolved in tetrahydrofuran, and the temperature of a reactor was cooled to -78°C. To this was slowly added dropwise 4.1 ml of butyllithium (2.5M in hexane), followed by stirring for 40 minutes. Thereafter, 27 g (103 mmol) of magnesium bromide ethylether complex was added and stirred for 40 minutes at the same temperature. 0.89 g (3.44 mmol) of 2R-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester obtained in PREPARATION 17 was dissolved in tetrahydrofuran and slowly added dropwise. Thereafter the temperature was gradually raised to room temperature. After stirring for about 2 hours, the product was diluted with ethyl acetate, washed once with aqueous saturated ammonium chloride solution and aqueous NaCl, respectively, dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 1) to give 0.7 g of the title compound in a yield of 65%.

1H NMR (CDCl₃) δ 5.29 (1H, m), 3.5-3.7 (2H, m), 2.6-2.8 (3H, m), 2.4-2.5 (1H, m), 1.9-2.1 (3H, m), 1.3-1.5 (9H, m)

Mass (m/e) 268 (M+1)

PREPARATION 51: Synthesis of 2-bromo-1-[2R-(5-tert-butyl-[1,3,4] oxadiazole-2R-carbonyl)-pyrrolidine-1-yl]-ethanone

0.72 g (2.22 mmol) of 2R-(5-tert-butyl-[1,3,4] oxadiazole-2R-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester obtained in PREPARATION 50 was dissolved in 34M HCl/EA, and the mixture was stirred for about 20 minutes and distilled off under reduced pressure. The resulting compound, (5-tert-butyl-[1,3,4]oxadiazole-2R-yl)-pyrrolidine-2R-yl-methanone), was dissolved in about 15 ml of dichloromethane and cooled to 0°C. To this were added dropwise 0.24
ml (2.8 mmol) of bromoacetyl bromide and 0.7 ml (5.0 mmol) of triethyl amine in sequence, followed by stirring for about 20 minutes. Water was added dropwise to quench the reaction, which was then extracted 3 times with dichloromethane. The extracted organic layer was separated, washed once with aqueous NaCl, dried over anhydrous magnesium sulfate, and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 2) to give 0.64 g of title compound in a yield of 83% (two steps).

\[ ^1H \text{NMR (CDCl}_3 \text{)} \delta 5.4 \text{ (1H, m), 3.8 (2H, Abq, J=16Hz), 37-39 (2H, m), 27 (3H, s), 2.5 \text{ (1H, m), 2.0-23 (3H, m)} \]

[1213] Mass (m/e) 302, 304 (M, M+2)

[1216] EXAMPLE 110: Synthesis of 2-tert-butylamino-1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrroolidine-1-yl]-ethanone

[1217] 30 mg of the title compound was obtained in a yield of 68% in the same manner as in EXAMPLE 1, except that 45 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-2S-carbonyl]-pyrroolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 27 µl of tert-butylamine were reacted.

[1218] Also, 30 mg of the title compound was obtained in a yield of 68% in the same manner as in EXAMPLE 1, except that 100 mg of 2-bromo-1-[2R-(5-tert-butyl-[1,3,4] oxadiazole-2R-carbonyl)-pyrroolidine-1-yl]-ethanone synthesized in PREPARATION 51 and 92 µl of tert-butylamine were reacted.

[1219] It was found that a diastereomeric mixture was obtained in the reaction using each single isomer synthesized in PREPARATIONS 13 and 51 as a starting material, and that the isomers had the similar activities to DPIV enzyme as will be demonstrated in EXPERIMENT later.

\[ ^1H \text{NMR (CDCl}_3 \text{)} \delta 5.4-5.5 \text{ (1H, m), 37-38 (1H, m), 36-37 (1H, m), 3.45 (2H, m), 2.4-2.5 (1H, m), 2.0-2.2 (4H, m), 1.5 (9H, s), 1.1 (9H, s)} \]

[1220] Mass (m/e) 337 (M+1)

[1222] EXAMPLE 111: Synthesis of 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrroolidine-1-yl]-ethanone

[1224] 31 mg of the title compound was obtained in a yield of 60% in the same manner as in EXAMPLE 1, except that 50 mg of 2-bromo-1-[2S-(5-tert-butyl-[1,3,4] oxadiazole-2S-carbonyl)-pyrroolidine-1-yl]-ethanone synthesized in PREPARATION 13 and 28 µl
of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

Also, 26 mg of the title compound was obtained in a yield of 25% in the same manner as in EXAMPLE 1, except that 100 mg of 2R-bromo-1-[2R-(5-tert-butyl-[1, 3,4]oxadiazole-2R-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 51 and 83 μl of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

It was found that a diastereomeric mixture was obtained in a reaction using each single isomer synthesized in PREPARATIONS 13 and 51 as a starting material, and that the isomers had the similar activities to DPIV enzyme as will be demonstrated in EXPERIMENT later.

PREPARATION 52: Synthesis of 4S-fluoro-2R-(5-tert-butyl-[1,3,4]oxadiazole-2R-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

1.04 g (825 mmol) of 2-tert-butyl-1,3,4-oxadiazole was dissolved in tetrahydrofuran, and the temperature of a reactor was cooled to -78°C. To this was slowly added dropwise 33 ml of butyllithium (2.5M in hexane), followed by stirring for 1 hour. To this was again slowly added dropwise a solution of 0.93 g (375 mmol) of 4S-fluoro-pyrrolidine-1,2R-dicarboxylic acid 1-tert-butyl ester 2R-methyl ester, which was dissolved in a small amount of tetrahydrofuran, followed by stirring for 2 hours at -40°C. After stirring for about 3 hours, the product was diluted with ethyl acetate, washed once with aqueous saturated ammonium chloride and aqueous NaCl, respectively, then dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 6 : 1) to give 551 mg of the title compound in a yield of 63%.

1H NMR (CDCl₃) δ 5.4-5.5 (1H, m), 3.7-3.8 (1H, m), 3.6-3.7 (1H, m), 3.45 (2H, m), 3.18 (2H, m), 2.4-2.5 (1H, m), 2.0-2.2 (3H, m), 1.5 (9H, s), 1.08 (3H, s), 1.07 (3H, s)

Mass (m/e) 353 (M+1)

PREPARATION 53: Synthesis of 2R-bromo-1-[4S-fluoro-2R-(5-tert-butyl-[1,3,4]oxadiazole-2R-carbonyl)-pyrrolidine-1-yl]-ethanone

404 mg (1.18 mmol) of 4S-fluoro-2R-(5-tert-butyl-[1,3,4] oxadiazole-2R-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester obtained in PREPARATION 52 was dissolved in 34M HCl/EA (20 ml), and the mixture was
stirred for about 5 minutes and distilled off under reduced pressure. The resulting compound, ((4S-fluoro-pyrrolidin-2R-yl)-(5-tert-butyl-[1,3,4] oxadiazole-2R-yl)-methanone), without purification, was dissolved in about 5 ml of dichloromethane and cooled to 0°C. To this were again added dropwise 0.12 ml (1.42 mmol) of bromoacetyl bromide and 036 ml (2.60 mmol) of triethyl amine in sequence, followed by stirring for about 30 minutes. Aqueous saturated ammonium chloride was added dropwise to quench the reaction which was then extracted twice with dichloromethane. The extracted organic layer was separated, washed once with aqueous NaCl, dried over anhydrous magnesium sulfate, and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to give 248 mg of title compound in a yield of 58%.

[1235] 1H NMR (CDCl₃) δ 5.5-5.4 (2H, m), 4.2-4.0 (2H, m), 39-38 (2H, m), 29-28 (1H, m), 23-22 (1H, m), 1.5-1.4 (9H, m)

[1236] Mass (m/e) 362,364 (M, M+2)

[1237] EXAMPLE 112: Synthesis of 2-tert-butilamino-1-[2-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone

[1239] 7.4 mg of the title compound was obtained in a yield of 50% in the same manner as in EXAMPLE 1, except that 15 mg of 2S-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4] oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 7 µl of tert-butylamine were reacted.

[1240] Also, 24.8 mg of the title compound was obtained in a yield of 47% in the same manner as in EXAMPLE 1, except that 54 mg of 2R-bromo-1-[4S-fluoro-2R-(5-tert-butyl-[1,3,4]oxadiazole-2R-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 53 and 33.0 mg of tert-butyl amine were reacted.

[1241] It was found that a diastereomeric mixture was obtained in a reaction using each single isomer synthesized in PREPARATIONS 35 and 53 as a starting material, and that the isomers had the similar activities to DPIV enzyme as will be demonstrated in EXPERIMENT later.

[1242] 1H NMR (CDCl₃) δ 53-5.7 (2H, m), 39-4.1(2H, m), 33-3.6 (2H, m), 27-2.8 (1H, m), 205-22 (1H, m), 1.49 (9H, m), 0.9-1.2 (9H, m)

[1243] Mass (m/e) 355 (M+1)

[1244]
EXAMPLE 113: Synthesis of 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[4S-fluoro-2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

10.5 mg of the title compound was obtained in a yield of 39% in the same manner as in EXAMPLE 1, except that 26 mg of 2S-bromo-1-[4S-fluoro-2S-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 35 and 14 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

Also, 27.2 mg of the title compound was obtained in a yield of 41% in the same manner as in EXAMPLE 1, except that 65 mg of 2R-bromo-1-[4S-fluoro-2R-(5-tert-butyl-[1,3,4]oxadiazole-2R-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 53 and 48 mg of 2-hydroxy-1,1-dimethyl-ethylamine were reacted.

It was found that a diastereomeric mixture was obtained in a reaction using each single isomer synthesized in PREPARATIONS 35 and 53 as a starting material, and that the isomers had the similar activities to DPIV enzyme as will be demonstrated in EXPERIMENT later.

1H NMR (CDCl₃) δ 53-5.7 (2H, m), 38-4.1 (2H, m), 30-36 (4H, m), 27-29 (1H, m), 21-23 (1H, m), 1.48 (9H, s), 1.03 (3H, s), 1.02 (3H, s)

Mass (m/e) 371 (M+1)

PREPARATION 54: Synthesis of 2S-(cyano-hydroxy-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

2.09 g (0.02 mol) of sodium bisulfate was dissolved in 100 ml of water and cooled to 0 ~ 4°C while stirring. To this was added dropwise to a solution of 4.00 g (0.02 mol) of 2S-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester which was dissolved in 10 ml of water and 5 ml of acetonitrile. After stirring at 0 ~ 4°C for 40 minutes, a solution of 0.98 g (0.02 mol) of sodium cyanide in 10 ml of water was added dropwise at 0 ~ 4 °C to the solution previously formed, and the mixture was stirred for 1 hour. To this was added 40 ml of diethyl ether and stirred at room temperature for 20 minutes. The organic layer was separated, and dried over anhydrous magnesium sulfate, then filtered off. The filtrated solution was distilled off under reduced pressure. Without further purification of the residue, 4.07 g of the title compound was obtained in a yield of 90%.

1H NMR (CDCl₃) δ 7.07-5.70 (1H, m), 4.6-4.5 (1H, m), 4.1 (1H, m), 3.5-3.4 (2H, m), 2.2 (1H, m), 2.1-1.8 (3H, m) 1.5-1.4 (9H, m)
[1255] Mass (m/e) 227 (M+1)

[1256]

[1257] **PREPARATION 55:** Synthesis of 2S-(carboxy-hydroxy-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

[1258] A mixed solution of 80 ml of concentrated hydrochloric acid and 80 ml of 1,4-dioxane was added to 2.40 (1.06 mmol) of 2S-(cyano-hydroxy-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 54 and stirred under reflux for 3 hours. After cooling to room temperature, the solvent and hydrochloric acid were removed under reduced pressure. The residue was diluted with 4.63 g (2.12 mmol) of di-tert-butyl dicarbonate and 80 ml of 1,4-dioxane, followed by addition of 22.03 ml (2.23 mmol) of aqueous 1N sodium hydroxide solution and stirring at room temperature for 15 hours. The reaction was diluted with 100 ml of ethyl acetate, and the product was washed with 15 ml of aqueous 1N HCl solution and aqueous NaCl in sequence. The organic layer obtained was dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (methanol : dichloromethane = 1 : 10) to give 1.43 g of the title compound in a yield of 55%.

[1259] $^1$H NMR (CDCl$_3$) δ 5.40 (2H, bs), 4.4-4.1 (2H, m), 3.5-3.4 (1H, m), 3.4-3.3 (1H, m), 2.24 (1H, bs), 2.1-1.9 (2H, m), 1.9-1.7 (1H, m), 1.47 (9H, s)

[1260] Mass (m/e) 246 (M+1)

[1261]

[1262] **PREPARATION 56:** Synthesis of 2S-[cyano-(1-ethoxy-ethoxy)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

[1263] 1.42 g (6.27 mol) of 2S-(cyano-hydroxy-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 54 was dissolved in 40 ml of methylene chloride, followed by addition of 0.72 ml (7.52 mmol) of ethylvinyl ether and 157 mg (0.63 mmol) of p-toluensulfonic acid pyridinate and stirring at room temperature for 2 hours. The reaction was concentrated under reduced pressure and purified by column chromatography (hexane : ethyl acetate = 10 : 1) to give 1.64 g of the title compound in a yield of 88%.

[1264] $^1$H NMR (CDCl$_3$) δ 5.2-4.5 (2H, m), 4.1-4.0 (1H, m), 3.7 (1H, m), 3.6-3.4 (2H, m), 2.2-2.0 (4H, m), 1.8 (1H, m), 1.5-1.4 (9H, m), 1.4-1.3 (3H, m), 13-1.2 (3H, m)

[1265] Mass (m/e) 299(M+1)

[1266]
PREPARATION 57: Synthesis of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

262 mg (377 mmol) of hydroxylamine hydrochloride was diluted with 10 ml of methanol, followed by addition of 316 mg (377 mmol) of sodium hydrocarbonate and stirring at room temperature for 20 minutes. 1.07 g (359 mmol) of 2S-[(cyano-(1-ethoxy-ethoxy)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 61, which was diluted with 10 ml of methanol, was added to the resulting solution and refluxed for 3 hours. The reaction was cooled to room temperature and filtered off to remove solid materials formed during the reaction. The filtrated solution obtained was concentrated under reduced pressure. The concentrate was purified by column chromatography (hexane : ethyl acetate = 2 : 1) to give 1.15 g of the title compound in a yield of 96%.

1H NMR (CDCl3) δ 8.50 (1H, bs), 5.1-5.0 (1H, m), 4.8-4.6 (2H, m), 4.2-4.1 (2H, m), 3.7-3.6 (1H, m), 3.5-3.3 (3H, m), 1.9-1.8 (4H, m), 1.47 (9H, s), 1.3-1.2 (3H, m), 1.2-1.1 (3H, m)

Mass (m/e) 331 (M+1)

PREPARATION 58: Synthesis of (2S,4S)-2-(cyano-hydroxy-methyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

308 g of the title compound was obtained in a yield of 95% in the same manner as in PREPARATION 54, except that 2.89 mg (133 mmol) of (2S,4S)-4-fluoro-2-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester, 138 g (133 mmol) of sodium bisulfate and 0.65 g (133 mmol) of sodium cyanide were used.

1H NMR (CDCl3) δ 6.10-5.85 (m, 1H), 5.32-5.15 (m, 1H), 4.65-4.63 (m, 1H), 3.76-3.60 (m, 2H), 2.51-2.23 (m, 2H), 1.52-1.44 (m, 9H).

Mass (m/e) 245 (M+1)

REPARATION 59: Synthesis of (2R,4S)-2-(cyano-hydroxy-methyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

777 mg of the title compound was obtained in a yield of 96% in the same manner as in PREPARATION 54, except that 723 mg (333 mmol) of (2R,4S)-4-fluoro-2-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester, 346 mg (333
mmol) of sodium bisulfate and 163 mg (333 mmol) of sodium cyanide were used.

[1279] Mass (m/e) 245 (M+1)

[1280]

[1281] **PREPARATION 60: Synthesis of**

(2S,4S)-2-[cyano-(1-ethoxy-ethoxy)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

[1282] 3.8 mg of the title compound was obtained in a yield of 95% in the same manner as in PREPARATION 56, except that 3.08 g (13.6 mmol) of (2S,4S)-2-[cyano-hydroxy-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 58, 1.45 ml (15.1 mmol) of ethylvinyl ether and 317 mg (12.6 mmol) of p-toluenesulfonic acid pyridinate were used.

[1283] $^1$H NMR (CDCl$_3$) δ 5.13-4.84 (m, 2H), 4.13-3.42 (m, 3H), 2.25-2.05 (m, 3H), 1.49-1.47 (m, 9H), 1.39-1.31 (m, 3H), 1.26-1.18 (m, 3H).

[1284] Mass (m/e) 317 (M+1)

[1285]

[1286] **PREPARATION 61: Synthesis of**

(2R,4S)-2-[cyano-(1-ethoxy-ethoxy)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

[1287] 650 mg of the title compound was obtained in a yield of 65% in the same manner as in PREPARATION 56, except that 777 mg (318 mmol) of (2R,4S)-2-[cyano-hydroxy-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 59, 0.40 ml (4.13 mmol) of ethylvinyl ether and 80 mg (0.32 mmol) of p-toluenesulfonic acid pyridinate were used.

[1288] $^1$H NMR (CDCl$_3$) δ 5.13-4.84 (m, 2H), 4.13-3.42 (m, 3H), 2.25-2.05 (m, 3H), 1.49-1.47 (m, 9H), 1.39-1.31 (m, 3H), 1.26-1.18 (m, 3H).

[1289] Mass (m/e) 317 (M+1)

[1290]

[1291] **PREPARATION 62: Synthesis of**

(2S,4S)-2-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

[1292] 3.64 g of the title compound was obtained in a yield of 87% in the same manner as in PREPARATION 57, except that 3.80 g (12.0 mmol) of (2S,4S)-2-[cyano-(1-ethoxy-ethoxy)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 60, 0.88 g (12.6 mmol) of hydroxyamine hydrochloride and 1.06 g (12.6 mmol) of sodium bicarbonate were used.
[1293] $^1$H NMR (CDCl$_3$) $\delta$ 5.32-5.25 (m, 1H), 5.18-5.10 (m, 1H), 5.00-4.99 (m, 2H), 4.76-4.70 (m, 2H), 4.25-4.12 (m, 2H), 4.00-3.50 (m, 4H), 2.60-2.35 (m, 1H), 2.25-2.00 (m, 1H), 1.86 (br s, 1H), 1.50-1.47 (m, 9H), 1.36-1.27 (m, 3H), 1.23-1.17 (m, 3H).

[1294] Mass (m/e) 350 (M+1)

[1295]

[1296] **PREPARATION 63: Synthesis of (2R,4S)-2-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-4-fluoro-pyrroldine-1-carboxylic acid tert-butyl ester**

[1297] 664 mg of the title compound was obtained in a yield of 93% in the same manner as in PREPARATION 60, except that 650 mg (2.05 mmol) of (2R,4S)-2-[(3-nitro-1-ethoxy-ethoxy)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 61, 157 mg (2.26 mmol) of hydroxylamine hydrochloride and 190 mg (2.26 mmol) of sodium bicarbonate were used.

[1298] $^1$H NMR (CDCl$_3$) $\delta$ 8.40 (br s, 1H), 5.23-5.05 (m, 1H), 4.93-4.60 (m, 2H), 4.40-4.10 (m, 2H), 4.00-3.62 (m, 2H), 3.51-3.40 (m, 2H), 2.40-2.20 (m, 2H), 1.48-1.44 (m, 9H), 1.33-1.24 (m, 3H), 1.21-1.15 (m, 3H).

[1299] Mass (m/e) 350 (M+1)

[1300]

[1301] **PREPARATION 64: Synthesis of 2S-[(1-ethoxy-ethoxy)-(5-methyl-[1,2,4] oxadiazole-3-yl)-methyl]pyrrolidine-1-carboxylic acid tert-butyl ester**

[1302] 504 mg (3.11 mmol) of 1,1-carbonyldiimidazole was added to 0.18 ml (3.11 mmol) of acetic acid which was diluted with 25 ml of dimethylformamide, followed by stirring at room temperature for 20 minutes. 860 mg (0.26 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, which was diluted with 20 ml of dimethylformamide, was added to the solution previously formed, and the resulting mixture was stirred at 70-110 $^\circ$C for 3 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The resulting concentrate was purified by column chromatography (hexane : ethyl acetate = 2 : 1) to give 570 mg of the title compound in a yield of 62%.

[1303] $^1$H NMR (CDCl$_3$) $\delta$ 5.4-5.3 (1H, m), 4.8-4.7 (1H, m), 4.2-4.1 (1H, m), 3.6-3.4 (4H, m), 2.6-2.5 (3H, m), 2.3-2.2 (1H, m), 2.1 (1H, m), 1.79 (bs, 2H), 1.5-1.4 (9H, m), 1.4-1.3 (3H, m), 1.1-1.0 (3H, m)

[1304] Mass (m/e) 356 (M+1)

[1305]
**PREPARATION 65:** Synthesis of (S)-2-[(1-ethoxy-ethoxy)-[1,2,4] oxadiazole-3-yl-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

111 mg of the title compound was obtained in a yield of 87% in the same manner as in PREPARATION 64, except that 182 mg (0.56 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 30.4 mg (0.66 mmol) of formic acid, and 107 mg (0.66 mmol) of 1,1-carbonyldiimidazole were used.

$^1$H NMR (CDCl$_3$) δ 8.71 (s, 1H), 5.50-5.36 (m, 1H), 4.83-4.78 (m, 1H), 4.20-4.09 (m, 1H), 3.67-3.10 (m, 3H), 2.91 (br s, 0.6H), 2.33-2.26 (m, 1H), 2.04 (br s, 1H), 1.84-1.80 (m, 1H), 1.70-1.60 (m, 1H), 1.52-1.45 (m, 9H), 1.35-1.24 (m, 3H), 1.16-1.07 (m, 3H).

Mass (m/e) 342 (M+1)

**PREPARATION 66:** Synthesis of (S)-2-[(5-tert-butyl-[1,2,4] oxadiazole-3-yl-methyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

140 mg (11.6 mmol) of pivaloyl chloride was added to 321 mg (9.70 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57 which was dissolved in 6 ml of pyridine. During the reaction, the temperature was raised to 110°C. After 3 hours, pyridine was removed under reduced pressure. The resulting concentrate was purified by column chromatography (hexane : ethyl acetate = 4 : 1) to give 209 mg of the title compound in a yield of 66%.

$^1$H NMR (CDCl$_3$) δ 4.95-4.71 (m, 1H), 4.37 (br s, 1H), 3.47-3.38 (m, 2H), 1.90-1.80 (m, 4H), 1.50-1.43 (m, 9H).

Mass (m/e) 342 (M+1)

**PREPARATION 67:** Synthesis of (S)-1-[(1-ethoxy-ethoxy)-(5-ethyl-[1,2,4]oxadiazole-3-yl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

250 mg of the title compound was obtained in a yield of 74% in the same manner as in PREPARATION 64, except that 302 mg (0.91 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 76.6 mg (1.09 mmol) of propionic acid and 177 mg (1.09 mmol) of 1,1-carbonyldiimidazole were used.

$^1$H NMR (CDCl$_3$) δ 5.38-5.26 (m, 1H), 4.84-4.77 (m, 1H), 4.30-4.00 (m, 1H),
370-3.55 (m, 1H), 350-340 (m, 2H), 2.94-2.88 (m, 3H), 2.40-2.00 (m, 2H), 1.89 (br s, 1H), 1.52-1.46 (m, 9H), 1.41-1.28 (m, 6H), 1.16-1.07 (m, 3H).

1319] Mass (m/e) 370 (M+1)

1320] **PREPARATION 68: Synthesis of (S)-2-[(5-cyclopropyl-[1,2,4]oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester**

1322] 780 mg of the title compound was obtained in a yield of 63% in the same manner as in PREPARATION 64, except that 1.08 g (3.26 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 0.31 ml (3.91 mmol) of cyclopropane carboxylic acid and 634 mg (3.91 mmol) of 1,1-carbonyldimidazole were used.

1323] $^1$H NMR (CDCl$_3$) δ 5.33-5.26 (m, 1H), 4.82-4.77 (m, 1H), 4.25-3.95 (m, 1H), 3.70-3.60 (m, 1H), 3.47-3.38 (m, 24H), 2.95 (br s, 0.6H), 2.30-2.00 (m, 4H), 1.80 (br s, 1H), 1.70 (br s, 1H), 1.53-1.47 (m, 9H), 1.33-1.09 (m, 9H).

1324] Mass (m/e) 382 (M+1)

1325] **PREPARATION 69: Synthesis of (S)-2-[(1-ethoxy-ethoxy)-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester**

1327] 94 mg of the title compound was obtained in a yield of 19% in the same manner as in PREPARATION 64, except that 377 mg (1.14 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 191 mg (1.36 mmol) of 4-fluorobenzoic acid and 221 mg (1.36 mmol) of 1,1-carbonyldimidazole were used.

1328] $^1$H NMR (CDCl$_3$) δ 8.18-8.15 (m, 2H), 7.27-7.19 (m, 2H), 5.48-5.31 (m, 1H), 4.88-4.83 (m, 1H), 4.30-4.10 (m, 1H), 3.85-3.64 (m, 1H), 3.51-3.43 (m, 2.5H), 3.00 (br s, 0.5H), 2.40-2.30 (m, 1H), 2.20-2.05 (m, 1H), 1.82-1.69 (m, 2H), 1.56-1.48 (m, 9H), 1.37-1.26 (m, 3H), 1.17-1.12 (m, 3H).

1329] Mass (m/e) 436 (M+1)

1330] **PREPARATION 70: Synthesis of (S)-2-[(1-ethoxy-ethoxy)-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-yl]-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester**
448 mg of the title compound was obtained in a yield of 52% in the same manner as in PREPARATION 64, except that 348 mg (1.05 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 166 mg (1.26 mmol) of 3-methoxy-2,2-dimethyl-propionic acid and 204 mg (1.26 mmol) of 1,1-carbonyldiimidazole were used.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 5.42-4.83 (m, 1H), 4.83-4.77 (m, 1H), 4.25-4.00 (m, 1H), 3.70-3.36 (m, 5H), 3.30-3.28 (m, 3H), 2.40-2.20 (m, 1H), 2.15-1.90 (m, 1H), 1.80 (br s, 1H), 1.54-1.33 (m, 15H), 1.31-1.21 (m, 4H), 1.14-1.10 (m, 3H). \]

Mass (m/e) 427 (M+1)

PREPARATION 71: Synthesis of (S)-2-[(5-cyclopentyl-[1,2,4] oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

475 mg of the title compound was obtained in a yield of 79% in the same manner as in PREPARATION 64, except that 488 mg (1.47 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 219 mg (1.77 mmol) of cyclopentane carboxylic acid and 287 mg (1.77 mmol) of 1,1-carbonyldiimidazole were used.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 5.38-5.29 (m, 1H), 4.82-4.78 (m, 1H), 4.30-4.00 (m, 1H), 3.69-3.60 (m, 1H), 3.47-3.32 (m, 3.5H), 2.90 (br s, 0.5H), 2.40-2.20 (m, 1H), 2.11-2.05 (m, 3H), 1.94-1.68 (m, 8H), 1.52-1.46 (m, 9H), 1.33-1.26 (m, 3H), 1.15-1.10 (m, 3H). \]

Mass (m/e) 410 (M+1)

PREPARATION 72: Synthesis of (S)-2-[(1-ethoxy-ethoxy)-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazole-3-yl]-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

415 mg of the title compound was obtained in a yield of 81% in the same manner as in PREPARATION 64, except that 426 mg (1.29 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 154 mg (1.54 mmol) of 1-methyl cyclopropyl carboxylic acid and 250 mg (1.54 mmol) of 1,1-carbonyldiimidazole were used.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 5.36-5.27 (m, 1H), 4.82-4.78 (m, 1H), 4.30-4.00 (m, 1H), 3.74-3.60 (m, 1H), 3.48-3.40 (m, 2.5H), 2.95 (br s, 0.5H), 2.40-2.00 (m, 2H), 2.80 (br
s, 1H), 270 (br s, 1H), 1.56-1.41 (m, 14H), 1.35-1.26 (m, 3H), 1.18-1.12 (m, 3H), 1.00 (s, 2H).

[1344] Mass (m/e) 396 (M+1)

[1345] PREPARATION 73: Synthesis of (S)-2-[(5-adamantane-1-yl-[1,2,4]
oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-pyrrolidine-1-carboxylic acid tert-
butyl ester

[1347] 449 mg of the title compound was obtained in a yield of 67% in the same manner as in PREPARATION 64, except that 470 mg (1.42 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 307 mg (1.70 mmol) of 1-adamantane carboxylic acid and 276 mg (1.70 mmol) of 1,1-carbonyldiimidazole were used.

[1348] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.40-530 (m, 1H), 4.82-4.75 (m, 1H), 4.30-4.00 (m, 1H), 3.72-3.61 (m, 1H), 3.59-3.40 (m, 2.5H), 2.90 (br s, 0.5H), 2.40-2.20 (m, 1H), 2.09-2.03 (m, 10H), 1.92-1.72 (m, 8H), 1.53-1.46 (m, 9H), 1.34-1.24 (m, 3H), 1.14-1.09 (m, 3H).

[1349] Mass (m/e) 476 (M+1)

[1350] PREPARATION 74: Synthesis of (S)-2-[(5-(1,1-dimethyl-propyl)-[1,2,4]
oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-pyrrolidine-1-carboxylic acid tert-
butyl ester

[1352] 316 mg of the title compound was obtained in a yield of 54% in the same manner as in PREPARATION 64, except that 473 mg (1.43 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 199 mg (1.71 mmol) of 2,2-dimethyl butyric acid and 277 mg (1.71 mmol) of 1,1-carbonyldiimidazole were used.

[1353] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.43-531 (m, 1H), 4.83-4.79 (m, 1H), 4.30-4.00 (m, 1H), 3.73-3.55 (m, 1H), 3.48-3.38 (m, 2.5H), 3.00-2.85 (m, 0.5H), 2.40-2.20 (m, 1H), 2.15-2.00 (m, 1H), 1.82-1.76 (m, 2H), 1.54-1.22 (m, 20H), 1.18-1.09 (m, 3H), 0.82-0.78 (m, 3H).

[1354] Mass (m/e) 412 (M+1)

[1355] PREPARATION 75: Synthesis of

(S)-2-[(1-ethoxy-ethoxy)-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-yl]-methyl]-
pyrrolidine-1-carboxylic acid tert-butyl ester

[1357] 450 mg of the title compound was obtained in a yield of 81% in the same manner as in PREPARATION 64, except that 422 mg (1.27 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 217 mg (1.53 mmol) of 1-methyl-cyclohexane carboxylic acid and 248 mg (1.53 mmol) of 1,1-carbonyldiimidazole were used.

[1358] 1H NMR (CDCl₃) δ 5.44-5.29 (m, 1H), 4.85-4.58 (m, 1H), 4.30-4.00 (m, 1H), 3.70-3.55 (m, 1H), 3.48-3.39 (m, 2.5H), 2.95-2.80 (m, 0.5H), 2.35-2.23 (m, 3H), 2.10-2.02 (m, 1H), 1.85-1.78 (m, 1H), 1.63-1.46 (m, 14H), 1.38-1.21 (m, 10H), 1.14-1.09 (m, 3H).

[1359] Mass (m/e) 438 (M+1)

[1360]

[1361] PREPARATION 76: Synthesis of (S)-2-[(1-ethoxy-ethoxy)-(5-(2-methoxy-phenyl)-[1,2,4]oxadiazole-3-yl]-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

[1362] 243 mg of the title compound was obtained in a yield of 48% in the same manner as in PREPARATION 64, except that 374 mg (1.13 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 205 mg (1.35 mmol) of 2-methoxybenzoic acid and 219 mg (1.35 mmol) of 1,1-carbonyldiimidazole were used.

[1363] 1H NMR (CDCl₃) δ 8.11-8.09 (m, 1H), 7.56-7.53 (m, 1H), 7.09-7.04 (m, 2H), 5.48-5.30 (m, 1H), 4.87-4.84 (m, 1H), 4.30-4.10 (m, 1H), 3.96 (s, 3H), 3.78-3.60 (m, 1H), 3.50-3.42 (m, 2.5H), 3.00 (br s, 0.5H), 2.40-2.25 (m, 1H), 2.11-1.98 (m, 1H), 1.83-1.80 (m, 2H), 1.68-1.65 (m, 9H), 1.37-1.31 (m, 3H), 1.17-1.12 (m, 3H).

[1364] Mass (m/e) 448 (M+1)

[1365]

[1366] PREPARATION 77: Synthesis of (S)-2-[[5-(2-acetoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-yl]-(1-ethoxy-ethoxy)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

[1367] 211 mg of the title compound was obtained in a yield of 45% in the same manner as in PREPARATION 64, except that 345 mg (1.04 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 200 mg (1.25 mmol) of
2-acetoxymethyl-2-methyl-propionic acid and 202 mg (1.25 mmol) of 1,1-carbonyldiimidazole were used.

\[1368\] 1H NMR (CDCl3) δ 5.44-5.31 (m, 1H), 4.83-4.80 (m, 1H), 4.26-4.09 (m, 4H), 3.71-3.68 (m, 1H), 3.46-3.41 (m, 2.5H), 3.00-2.80 (m, 0.5H), 2.35-2.20 (m, 1H), 2.04-2.00 (m, 5H), 1.80-1.60 (m, 2H), 1.53-1.45 (m, 15H), 1.34-1.24 (m, 3H), 1.15-1.09 (m, 3H).

[1369] Mass (m/e) 456 (M+1)

[1370]

[1371]  **PREPARATION 78: Synthesis of (2S,4S)-2-[(1-ethoxy-ethoxy)-(5-methyl-[1,2,4]oxadiazole-3-yl)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1372] 940 mg of the title compound was obtained in a yield of 83\% in the same manner as in PREPARATION 64, except that 1.05 g (301 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 217 mg (361 mmol) of acetic acid and 585 mg (361 mmol) of 1,1-carbonyldiimidazole were used.

[1373] 1H NMR (CDCl3) δ 5.31-5.17 (m, 1H), 5.05-4.85 (m, 1H), 4.71-4.69 (m, 1H), 4.40-4.28 (m, 2H), 3.90-3.39 (m, 4H), 2.70-2.58 (m, 4H), 2.30-2.11 (m, 1H), 1.51 (br s, 3H), 1.36-1.24 (m, 9H), 1.16-1.01 (m, 3H).

[1374] Mass (m/e) 374 (M+1)

[1375]

[1376]  **PREPARATION 79: Synthesis of (2S,4S)-2-[(5-tert-butyl-[1,2,4]oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1377] 490 mg of the title compound was obtained in a yield of 48\% in the same manner as in PREPARATION 64, except that 860 mg (2.46 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 301 mg (2.95 mmol) of trimethyl acetic acid and 479 mg (2.95 mmol) of 1,1-carbonyldiimidazole were used.

[1378] 1H NMR (CDCl3) δ 5.31-5.28 (m, 1H), 5.15-5.14 (m, 1H), 4.80-4.75 (m, 1H), 4.33 (br s, 1H), 3.75-3.37 (m, 5H), 2.70-2.10 (m, 2H), 1.52-1.51 (m, 1H), 1.44-1.23 (m, 20H), 1.12-1.00 (m, 3H).

[1379] Mass (m/e) 416 (M+1)

[1380]

[1381]  **PREPARATION 80: Synthesis of**
(2S,4S)-2-[(5-(1,1-dimethyl-propyl)-(1,2,4]oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

365 mg of the title compound was obtained in a yield of 77% in the same manner as in PREPARATION 64, except that 385 mg (1.10 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 153 mg (1.32 mmol) of 2,2-dimethyl butyric acid and 214 mg (132 mmol) of 1,1-carbonyldiimidazole were used.

Mass (m/e) 430 (M+1)

[1384]

PREPARATION 81: Synthesis of (2S,4S)-2-[(1-ethoxy-ethoxy)-(5-(1-methyl-cyclohexyl)-1,2,4]oxadiazole-3-yl)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

313 mg of the title compound was obtained in a yield of 62% in the same manner as in PREPARATION 64, except that 374 mg (1.07 mmol) of 2S-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 57, 208 mg (1.28 mmol) of 1-methyl-cyclohexane carboxylic acid and 208 mg (1.28 mmol) of 1,1-carbonyldiimidazole were used.

Mass (m/e) 456 (M+1)

[1388]

PREPARATION 82: Synthesis of (2R,4S)-2-[(5-tert-butyl-[1,2,4] oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

325 mg of the title compound was obtained in a yield of 51% in the same manner as in PREPARATION 64, except that 539 mg (1.54 mmol) of (2R,4S)-2-[(1-ethoxy-ethoxy)-(N-hydroxycarbamimidoyl)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 63, 189 mg (1.85 mmol) of trimethyl acetic acid and 300 mg (1.85 mmol) of 1,1-carbonyldiimidazole were used.

^1H NMR (CDCl \textsubscript{3}) \( \delta \) 5.51-5.29 (m, 1H), 4.84-4.76 (m, 2H), 4.50-4.10 (m, 1H), 4.00-3.62 (m, 1H), 3.52-3.37 (m, 2H), 1.90-2.30 (m, 2H), 2.20-2.10 (m, 1H), 1.52-1.38 (m, 17H), 1.30-1.24 (m, 3H), 1.13-1.08 (m, 3H).

Mass (m/e) 416 (M+1)
PREPARATION 83: Synthesis of 2S-[hydroxy-(3-methyl-[1,2,4]
  oxadiazole-5-yl)-methyl]pyrrolidine-1-carboxylic acid tert-butyl ester

1.12 g (6.98 mmol) of 1,1-carbonyldiimidazole was added to 810 mg (330 mmol)
of 2S-(carboxy-hydroxy-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester
synthesized in PREPARATION 55, which was diluted with 40 ml of dimethy-
formamide, and the resulting mixture was stirred at room temperature for 20 minutes.
To this was added 514 mg (6.93 mmol) of acetamidoxim diluted with 30 ml of dimet
hylformamide, followed by stirring at 70-110°C for 3 hours. The reaction was cooled
to room temperature, from which solvent was removed under reduced pressure. The
concentrate obtained was purified by column chromatography (hexane : ethyl acetate =
2 : 1) to give 340 mg of the title compound in a yield of 36%.

1H NMR (CDCl3) δ 6.4-6.0 (1H, m), 5.1-4.8 (1H, m), 4.4-4.2 (1H, m), 3.6 (2H, m),
2.40 (3H, m), 2.0-1.8 (4H, m), 1.5-1.4 (9H, m)

Mass (m/e) 285 (M+1)

PREPARATION 84: Synthesis of 2S-(3-methyl-[1,2,4] oxadiazole-
5-carbonyl)pyrrolidine-1-carboxylic acid tert-butyl ester

6 ml of a solution of Dess-Martin periodinate in 15% methylene chloride was
added to 340 mg (1.20 mmol) of 2S-[hydroxy-(3-methyl-[1,2,4] oxadiazole-
5-yl)-methyl]pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in
PREPARATION 83, which was diluted with 15 ml of dichloromethane, and the
resulting mixture was stirred at 50-80°C for 2 hours. The solvent was removed under
reduced pressure. The concentrate obtained was purified by column chromatography
(hexane : ethyl acetate = 3 : 1) to give 73 mg of the title compound in a yield of 22%.

1H NMR (CDCl3) δ 5.2-5.0 (1H, m), 37-3.6 (2H, m), 2.5 (3H, m), 2.4-23 (1H, m),
2.1-1.9 (3H, m), 1.4-13 (9H, m)

Mass (m/e) 282 (M+1)

PREPARATION 85: Synthesis of 2S-[hydroxyl-(5-methyl-[1,2,4]
oxadiazole-3-yl)-methyl]pyrrolidine-1-carboxylic acid tert-butyl ester

40 mg (0.16 mmol) of p-toluenesulfonic acid pyridate was added to 570 mg (1.60
mmol) of 2S-[(1-ethoxy-ethoxy)-(5-methyl-[1,2,4]oxadiazole-3-yl)-methyl]
pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 64,
which was diluted with 30 ml of ethanol, followed by stirring at 50-80°C for 2 hours.
The reaction was cooled to room temperature, from which the solvent was removed
under reduced pressure. The concentrate obtained was purified by column chromatography (hexane : ethyl acetate = 2:1) to give 410 mg of the title compound in a yield of 89%.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 6.08-5.92 (1H, m), 4.98-4.69 (1H, m), 433 (1H, bs), 3.48-3.39 (2H, m), 2.60-2.58 (3H, m), 2.05-1.63 (4H, m), 1.49-1.47 (9H, m) \]

Mass (m/e) 285 (M+1)

**PREPARATION 86: Synthesis of 2S-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)pyrrolidine-1-carboxylic acid tert-butyl ester**

8 ml of solution of Dess-Martin periodinane in 15% methylene chloride was added to 410 mg (1.45 mmol) of 2S-[hydroxyl-(5-methyl-[1,2,4]oxadiazole-3-yl)-methyl] pyrrolidine-1-carboxylic acid tert-butyl ester, which was diluted with 30 ml of dichloromethane, followed by stirring at 50-80°C for 2 hours. The solvent was removed under reduced pressure. The concentrate obtained was purified by column chromatography (hexane : ethyl acetate = 3:1) to give 395 mg of the title compound in a yield of 97%.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 5.24-5.07 (1H, m), 3.67-3.49 (2H, m), 2.71-2.68 (3H, m), 2.40-2.35 (1H, m), 2.06-1.93 (3H, m), 1.44-1.30 (9H, m) \]

Mass (m/e) 282 (M+1)

**PREPARATION 87: Synthesis of (S)-2-((1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester**

530 mg (1.55 mmol) of (S)-2-[(1-ethoxy-ethoxy)-[1,2,4]oxadiazole-3-yl-methyl] pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 65 was dissolved in 20 ml of ethanol, followed by addition of 25 mg (0.16 mmol) of p-toluenesulfonylic acid pyridate and stirring at 50-60°C for 2 hours. The reaction was cooled to room temperature, from which the solvent was removed to obtain 352 mg of hydroxyl compound. The hydroxyl compound obtained, without further purification, was diluted with methylene chloride, and 8 ml of Dess-Martin periodinane in 15% methylene chloride was added thereto at room temperature. After stirring for 1.5 hours, the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane : methyl acetate = 4:1) to give 340 mg of the title compound in a yield of 82%.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 5.25-5.08 (m, 1H), 3.69-3.51 (m, 4H), 2.41-2.39 (m, 1H), 2.10-1.95 (m, 3H), 1.44-1.28 (m, 9H). \]
[1417] Mass (m/e) 268 (M+1)

[1418] 

[1419] **PREPARATION 88: Synthesis of (S)-2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1420] 209 mg (0.64 mmol) of (S)-2-[(5-tert-butyl-[1,2,4] oxadiazole-3-yl-methyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 66 was dissolved in 10 ml of methylene chloride, and 5 ml of Dess-Martin periodinane in 15% methylene chloride was added thereto at room temperature. After stirring for 1.5 hours, the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane : methyl acetate = 3 : 1) to give 130 mg of the title compound in a yield of 63%.

[1421] $^1$H NMR (CDCl$_3$) $\delta$ 5.22-5.19 (m, 1H), 3.64-3.46 (m, 2H), 2.36-2.33 (m, 1H), 2.05-1.90 (m, 3H), 1.46-1.22 (m, 9H).

[1422] Mass (m/e) 324 (M+1)

[1423] 

[1424] **PREPARATION 89: Synthesis of (S)-2-(5-ethyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1425] 170 mg of the title compound was obtained in a yield of 85% in the same manner as in PREPARATION 87, except that 250 mg (0.68 mmol) of (S)-2-[(1-ethoxy-ethoxy)-(5-ethyl-[1,2,4]oxadiazole-3-yl)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 67, 17 mg (0.07 mmol) of p-toluenesulfonic acid pyridate and 5.5 ml of Dess-Martin periodinane in 15% methylene chloride were used.

[1426] $^1$H NMR (CDCl$_3$) $\delta$ 5.25-5.07 (m, 1H), 3.67-3.58 (m, 2H), 3.05-2.99 (m, 2H), 2.40-2.30 (m, 1H), 2.09-1.92 (m, 3H), 1.47-1.24 (m, 11H).

[1427] Mass (m/e) 296 (M+1)

[1428] 

[1429] **PREPARATION 90: Synthesis of (S)-2-(5-cyclopropyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1430] 605 mg of the title compound was obtained in a yield of 97% in the same manner as in PREPARATION 87, except that 780 mg (2.04 mmol) of (S)-2-[(5-cyclopropyl-[1,2,4]oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 68, 51.4 mg (0.21 mmol) of p-toluenesulfonic acid pyridate and 9 ml of Dess-Martin periodinane in 15% methylene chloride were used.
[1431] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.30-5.04 (m, 1H), 3.66-3.54 (m, 2H), 2.32-2.27 (m, 2H), 2.05-1.92 (m, 3H), 1.43 (s, 4H), 1.35-1.26 (m, 9H).

[1432] Mass (m/e) 308 (M+1)

[1433]

[1434] **PREPARATION 91: Synthesis of (S)-2-[5-(4-fluoro-phenyl)-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1435] 76 mg of the title compound was obtained in a yield of 97% in the same manner as in PREPARATION 87, except that 94 mg (0.22 mmol) of (S)-2-\(\{1\)-ethoxy-ethoxy\}-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-methyl\]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 69, 5.4 mg (0.022 mmol) of p-toluenesulfonic acid pyridate and 3 ml of Dess-Martin periodinane in 15% methylene chloride were used.

[1436] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.27-8.22 (m, 2H), 7.28-7.22 (m, 1H), 5.29-5.12 (m, 1H), 3.71-3.51 (m, 2H), 2.45-2.40 (m, 1H), 2.11-1.95 (m, 3H), 1.46-1.31 (m, 9H).

[1437] Mass (m/e) 362 (M+1)

[1438]

[1439] **PREPARATION 92: Synthesis of (S)-2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1440] 180 mg of the title compound was obtained in a yield of 93% in the same manner as in PREPARATION 87, except that 234 mg (0.55 mmol) of (S)-2-\(\{1\)-ethoxy-ethoxy\}-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-yl]-methyl\]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 70, 138 mg (0.055 mmol) of p-toluenesulfonic acid pyridate and 7 ml of Dess-Martin periodinane in 15% methylene chloride were used.

[1441] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.24-5.04 (m, 1H), 3.65-3.56 (m, 4H), 3.31-3.28 (m, 4H), 2.37-2.35 (m, 1H), 2.09-1.93 (m, 3H), 1.48-1.44 (m, 9H), 1.29-1.26 (m, 6H).

[1442] Mass (m/e) 354 (M+1)

[1443]

[1444] **PREPARATION 93: Synthesis of (S)-2-(5-cyclopentyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1445] 368 mg of the title compound was obtained in a yield of 95% in the same manner as in PREPARATION 87, except that 475 mg (1.16 mmol) of (S)-2-\(\{5\)-cyclopentyl-[1,2,4]oxadiazole-3-yl\}-\(\{1\)-ethoxy-ethoxy\}-methyl\]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 71, 29 mg (0.12
mmol) of p-toluenesulfonic acid pyridate and 12 ml of Dess-Martin periodinane in 15% methylene chloride were used.

[1446] $^1$H NMR (CDCl$_3$) $\delta$ 5.25-5.06 (m, 1H), 3.66-3.42 (m, 3H), 2.40-230 (m, 1H), 235 (br s, 2H), 2.05-1.94 (m, 5H), 1.86-1.84 (m, 2H), 1.74-1.72 (m, 2H), 1.44-1.29 (m, 9H).

[1447] Mass (m/e) 336 (M+1)

[1448] **PREPARATION 94: Synthesis of (S)-2-[5-(1-methyl-cyclopropyl)-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1450] 275 mg of the title compound was obtained in a yield of 82% in the same manner as in PREPARATION 87, except that 415 mg (1.05 mmol) of (S)-2-[(1-ethoxy-ethoxy)-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazole-3-yl]-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 72, 26.4 mg (0.11 mmol) of p-toluenesulfonic acid pyridate and 10 ml of Dess-Martin periodinane in 15% methylene chloride were used.

[1451] $^1$H NMR (CDCl$_3$) $\delta$ 5.23-5.04 (m, 1H), 3.66-3.55 (m, 2H), 2.40-230 (m, 1H), 2.05-1.93 (m, 3H), 1.62-1.60 (m, 3H), 1.52-1.50 (m, 2H), 1.43 (s, 3H), 1.30-1.26 (m, 6H), 1.12-1.07 (m, 2H).

[1452] Mass (m/e) 336 (M+1)

[1453] **PREPARATION 95: Synthesis of (S)-2-(5-adamantane-1-yl-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1455] 400 mg of the title compound was obtained in a yield of 99% in the same manner as in PREPARATION 87, except that 477 mg (1.00 mmol) of (S)-2-[(5-adamantane-1-yl-[1,2,4]oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 73, 25.2 mg (0.10 mmol) of p-toluenesulfonic acid pyridate and 6 ml of Dess-Martin periodinane in 15% methylene chloride were used.

[1456] $^1$H NMR (CDCl$_3$) $\delta$ 5.24-5.04 (m, 1H), 3.68-3.67 (m, 2H), 2.40-230 (m, 1H), 2.12-1.90 (m, 10H), 1.80-1.75 (m, 5H), 1.44 (s, 3H), 132-1.24 (m, 9H).

[1457] Mass (m/e) 402 (M+1)

[1458] **PREPARATION 96: Synthesis of (S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester**

[1460] 260 mg of the title compound was obtained in a yield of 97% in the same manner
as in PREPARATION 87, except that 316 mg (0.77 mmol) of
(S)-2-[[5-(1,1-dimethyl-propyl)]=[1,2,4]oxadiazole-3-yl]-[1-ethoxy-ethoxy]-methyl]-pyrr
rrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 74, 193
mg (0.08 mmol) of p-toluene sulfonic acid pyridate and 9 ml of Dess-Martin pe-
riodinane in 15% methylene chloride were used.

[1461] 1H NMR (CDCl₃) δ 5.08-5.05 (m, 1H), 3.65-3.58 (m, 2H), 237-234 (m, 1H),
2.06-1.94 (m, 3H), 1.84-1.81 (m, 2H), 1.45-1.43 (m, 9H), 1.28 (s, 6H), 0.85-0.80 (m,
3H).

[1462] Mass (m/e) 338 (M+1)

[1463]

[1464] PREPARATION 97: Synthesis of (S)-2-[[5-(1-methyl-cyclohexyl)]=[1,2,4]oxadiazole-3-carbonyl]-pyrrrolidine-1-carboxylic acid tert-butyl ester

[1465] 330 mg of the title compound was obtained in a yield of 88% in the same manner
as in PREPARATION 87, except that 450 mg (1.03 mmol) of
(S)-2-[(1-ethoxy-ethoxy)-[5-(1-methyl-cyclohexyl)]=[1,2,4]oxadiazole-3-yl]-methyl]-p
yrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 75, 26 mg
(0.10 mmol) of p-toluene sulfonic acid pyridate and 14 ml of Dess-Martin periodinane
in 15% methylene chloride were used.

[1466] 1H NMR (CDCl₃) δ 5.08-5.04 (m, 1H), 3.67-3.59 (m, 2H), 2.40-2.27 (m, 3H), 2.10
(s, 3H), 2.09-2.00 (m, 3H), 1.64-1.53 (m, 5H), 1.44-1.37 (m, 9H), 1.28-1.24 (m, 2H).

[1467] Mass (m/e) 364 (M+1)

[1468]

[1469] PREPARATION 98: Synthesis of (S)-2-[[5-(2-methoxy-phenyl)]=[1,2,4]oxadiazole-3-carbonyl]-pyrrrolidine-1-carboxylic acid tert-butyl ester

[1470] 167 mg of the title compound was obtained in a yield of 83% in the same manner
as in PREPARATION 87, except that 243 mg (0.54 mmol) of
(S)-2-[(1-ethoxy-ethoxy)-[5-(2-methoxy-phenyl)]=[1,2,4]oxadiazole-3-yl]-methyl]-pyrr
rolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 76, 14 mg
(0.05 mmol) of p-toluene sulfonic acid pyridate and 7.5 ml of Dess-Martin periodinane
in 15% methylene chloride were used.

[1471] 1H NMR (CDCl₃) δ 8.21-8.15 (m, 1H), 7.63-7.57 (m, 1H), 7.14-7.08 (m, 2H),
5.34-5.16 (m, 1H), 4.02-4.00 (m, 3H), 3.73-3.59 (m, 2H), 2.44-2.39 (m, 1H), 2.14-1.96
(m, 9H), 1.46-1.33 (m, 9H).

[1472] Mass (m/e) 374 (M+1)

[1473]
PREPARATION 99: Synthesis of (S)-2-[5-(2-acetoxy-1,1-dimethyl-ethyl)\{-1,2,4\}oxadiazole-3-carbonyl\}-pyrrolidine-1-carboxylic acid tert-butyl ester

166 mg of the title compound was obtained in a yield of 95% in the same manner as in PREPARATION 87, except that 211 mg (0.46 mmol) of (S)-2-[5-(2-acetoxy-1,1-dimethyl-ethyl)\{-1,2,4\}oxadiazole-3-yl]-\{1-ethoxy-ethoxy\}-m ethyl\}-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 77, 11.6 mg (0.05 mmol) of p-toluenesulfonic acid pyridate and 5 ml of Dess-Martin periodinane in 15% methylene chloride were used.

\(^1\)H NMR (CDCl\(_3\)) \(\delta 5.25-5.03 \text{ (m, 1H), 431-430 \text{ (m, 3H), 368-346 (m, 2H),} \)
\(2.41-235 \text{ (m, 1H), 208-1.92 \text{ (m, 6H), 1.52-1.44(m, 9H), 1.28-1.26 (m, 6H).} \)

Mass (m/e) 382 (M+1)

PREPARATION 100: Synthesis of (2S,4S)-4-fluoro-2-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

800 mg of the title compound was obtained in a yield of 96% in the same manner as in PREPARATION 87, except that 1.04 g (279 mmol) of (2S,4S)-2-\{(1-ethoxy-ethoxy)-(5-methyl-[1,2,4]oxadiazole-3-yl)-methyl\}-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 78, 70 mg (0.28 mmol) of p-toluenesulfonic acid pyridate and 17 ml of Dess-Martin periodinane in 15% methylene chloride were used.

\(^1\)H NMR (CDCl\(_3\)) \(\delta 530-5.27 \text{ (m, 1H), 5.19-5.16 \text{ (m, 1H), 397-371 \text{ (m, 2H),} \)
\(271-2.62 \text{ (m, 3H), 2.59-2.52 \text{ (m, 2H), 1.48-1.36 (m, 9H).} \)

PREPARATION 101: Synthesis of (2S,4S)-2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

175 mg of the title compound was obtained in a yield of 88% in the same manner as in PREPARATION 87, except that 242 mg (0.58 mmol) of (2S,4S)-2-\{(5-tert-butyl-[1,2,4]oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl\}-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 79, 14.6 mg (0.06 mmol) of p-toluenesulfonic acid pyridate and 10 ml of Dess-Martin periodinane in 15% methylene chloride were used.

\(^1\)H NMR (CDCl\(_3\)) \(\delta 532-5.28 \text{ (m, 1H), 5.20-5.17 \text{ (m, 1H), 4.00-3.87 (m, 1H),} \)
\(3.84-3.68 \text{ (m, 1H), 272-2.69 \text{ (m, 3H), 2.67-2.53 (m, 2H), 1.48-1.36 (m, 9H).} \)

Mass (m/e) 342 (M+1)
PREPARATION 102: Synthesis of (2S,4S)-2-[5-(1,1-dimethyl-thyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

261 mg of the title compound was obtained in a yield of 86% in the same manner as in PREPARATION 87, except that 365 mg (0.85 mmol) of (2S,4S)-2-[[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-yl]-[1-ethoxy-ethoxy]-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 80, 21 mg (0.09 mmol) of p-toluenesulfonic acid pyridate and 9 ml of Dess-Martin periodinane in 15% methylene chloride were used.

$^1$H NMR (CDCl$_3$) δ 532-5.29 (m, 1H), 5.19-5.16 (m, 1H), 4.00-371 (m, 2H), 2.65-2.55 (m, 2H), 2.10 (s, 3H), 1.87-1.79 (m, 2H), 1.50-1.44 (m, 9H), 1.35 (s, 4H), 1.18 (s, 1H), 0.91-0.81 (m, 3H).

Mass (m/e) 356 (M+1)

PREPARATION 103: Synthesis of (2S,4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

237 mg of the title compound was obtained in a yield of 90% in the same manner as in PREPARATION 87, except that 313 mg (0.69 mmol) of (2S,4S)-2-[(1-ethoxy-ethoxy)-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-yl]-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 81, 17 mg (0.07 mmol) of p-toluenesulfonic acid pyridate and 9 ml of Dess-Martin periodinane in 15% methylene chloride were used.

$^1$H NMR (CDCl$_3$) δ 533-530 (m, 1H), 5.19-5.16 (m, 1H), 397-371 (m, 2H), 2.63-2.56 (m, 2H), 2.27-2.25 (m, 2H), 2.05-2.00 (m, 1H), 1.63-1.48 (m, 8H), 1.43-1.35 (m, 9H), 1.28-1.21 (m, 2H).

Mass (m/e) 382 (M+1)

PREPARATION 104: Synthesis of (2R,4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

238 mg of the title compound was obtained in a yield of 82% in the same manner as in PREPARATION 87, except that 325 mg (0.849 mmol) of (2R,4S)-2-[(5-tert-butyl-[1,2,4]oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 82, 21.0
mg (0.09 mmol) of p-toluenesulfonic acid pyridate and 9 ml of Dess-Martin periodinane in 15\% methylene chloride were used.

\[ ^1H \text{NMR (CDCl}_3 \text{) } \delta 538-534 (m, 1H), 5.23-5.16 (m, 1H), 4.03-370 (m, 2H), 271-2.65 (m, 1H), 232-2.05 (m, 1H), 1.48-1.24 (m, 18H). \]

Mass (m/e) 342 (M+1)

**PREPARATION 105: Synthesis of 2-bromo-[2S-(3-methyl-[1,2,4] oxadiazole-5-carbonyl)-pyrrolidine-1-yl]-ethanone**

8 ml of 3N HCl/methyl acetate solution was added to 73 mg (0.26 mmol) of 2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 83, followed by stirring at room temperature for 10 minutes. The residual hydrochloric acid was removed by concentration under reduced pressure. The resulting hydrochloride salt was diluted with 10 ml of methylene chloride, then 0.025 ml (0.28 mmol) of bromoacetyl bromide and 0.072 ml (0.51 mmol) of triethylamine were slowly added thereto in sequence in water bath. After stirring for 1 hour in water bath, the temperature was slowly raised to room temperature over 30 minutes. The reaction was diluted with 60 ml of methyl acetate, and the product was washed with aqueous ammonium chloride. The organic layer obtained was dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 1) to give 40 mg of the title compound in a yield of 51\% (two steps).

\[ ^1H \text{NMR (CDCl}_3 \text{) } \delta 5.4-5.3 (1H, m), 3.9-3.8 (4H, m), 2.51 (3H, s), 2.6-2.4 (1H, m), 2.2-2.1 (3H, m) \]

Mass (m/e) 302, 304 (M, M+2)

**PREPARATION 106: Synthesis of 2-bromo-[2S-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone**

30 ml of 3N HCl/ethyl acetate solution was added to 395 mg (1.40 mmol) of 2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 86, followed by stirring at room temperature for 10 minutes. The residual hydrochloric acid was removed by concentration under reduced pressure. The resulting hydrochloride salt was diluted with 40 ml of methylene chloride, then 0.13 ml (1.56 mmol) of bromoacetyl bromide and 0.37 ml (2.69 mmol) of triethylamine were slowly added thereto in sequence in water bath.
After stirring for 1 hour in water bath, the temperature was slowly raised to room temperature over a period of 30 minutes. The product was diluted with 60 ml of methyl acetate and washed with aqueous ammonium chloride solution. The organic layer obtained was dried over anhydrous magnesium sulfate and filtered off. The filtrated solution was distilled off under reduced pressure. The residue was purified by column chromatography (hexane : ethyl acetate = 1 : 1) to give 250 mg of the title compound in a yield of 65% (two steps).

\[ 1^H \text{NMR (CDCl}_3 \delta 538-531 (1H, m), 386 (2H, ABq, J=10.8Hz), 379-373 (2H, m), 2.69 (3H, s), 2.42-235 (1H, m), 2.18-2.03 (3H, m) } \]

[1511] Mass (m/e) 302, 304 (M, M+2)

[1512]

[1513] **PREPARATION 107: Synthesis of 2-bromo-1-[(S)-2-[1,2,4] oxadiazole-3-carboxyl]-pyrrolidine-1-yl]-ethanone**

[1514] 87 mg of the title compound was obtained in a yield of 13% in the same manner as in PREPARATION 106, except that 61 mg (0.23 mmol) of (S)-2-[(1,2,4] oxadiazole-3-carboxyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 87, 7 ml of 3N HCl/methyl acetate solution, 24 µl (0.27 mmol) of bromoacetyl bromide and 66 µl (0.48 mmol) of triethylamine were used.

\[ 1^H \text{NMR (CDCl}_3 \delta 891 (s, 1H), 5.41-538 (m, 1H), 4.11-374 (m, 4H), 2.44-237 (m, 1H), 2.20-2.03 (m, 3H). } \]

[1516] Mass (m/e) 288, 290 (M, M+2)

[1517]

[1518] **PREPARATION 108: Synthesis of 2-bromo-1-[(S)-2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone**

[1519] 89 mg of the title compound was obtained in a yield of 64% in the same manner as in PREPARATION 106, except that 130 mg (0.40 mmol) of (S)-2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 88, 10 ml of 3N HCl/methyl acetate solution, 38 µl (0.44 mmol) of bromoacetyl bromide and 110 µl (0.80 mmol) of triethylamine were used.

\[ 1^H \text{NMR (CDCl}_3 \delta 5.42-539 (m, 1H), 4.07-371 (m, 4H), 2.42-237 (m, 1H), 2.17-2.03 (m, 3H), 1.51-1.45 (m, 9H). } \]

[1521] Mass (m/e) 344, 346 (M, M+2)

[1522]

[1523] **PREPARATION 109: Synthesis of 2-bromo-1-[(S)-2-(5-ethyl-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone**
[1524] 159 mg of the title compound was obtained in a yield of 87% in the same manner as in PREPARATION 106, except that 170 mg (0.58 mmol) of (S)-2-(5-ethyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 89, 15 ml of 3N HCl/methyl acetate solution, 90 μl (1.02 mmol) of bromoacetyl bromide and 250 μl (1.78 mmol) of triethylamine were used.

[1525] 1H NMR (CDCl₃) δ 539-532 (m, 1H), 393-373 (m, 4H), 301 (q, 2H, J=7.6Hz), 2.43-2.36 (m, 1H), 2.17-2.01 (m, 3H), 1.44 (t, 3H, J=7.6Hz).

[1526] Mass (m/e) 316, 318 (M, M+2)

[1527]

[1528] PREPARATION 110: Synthesis of 2-bromo-1-[(S)-2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

[1529] 390 mg of the title compound was obtained in a yield of 61% in the same manner as in PREPARATION 106, except that 600 mg (1.95 mmol) of (S)-2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 90, 30 ml of 3N HCl/methyl acetate solution, 220 μl (2.57 mmol) of bromoacetyl bromide and 820 μl (4.71 mmol) of N,N-diisopropylethylamine were used.

[1530] 1H NMR (CDCl₃) δ 539-531 (m, 1H), 391-374 (m, 4H), 238-226 (m, 2H), 2.15-2.03 (m, 3H), 1.35-1.28 (m, 4H).

[1531] Mass (m/e) 328, 330 (M, M+2)

[1532]

[1533] PREPARATION 111: Synthesis of 2-bromo-1-[(S)-2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[1534] 48 mg of the title compound was obtained in a yield of 56% in the same manner as in PREPARATION 106, except that 80.8 mg (0.22 mmol) of (S)-2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 91, 4.8 ml of 3N HCl/methyl acetate solution, 23 μl (2.57 mmol) of bromoacetyl bromide and 90 μl (0.49 mmol) of N,N-diisopropylethylamine were used.

[1535] 1H NMR (CDCl₃) δ 825-821 (m, 2H), 7.27-7.22 (m, 1H), 5.46-5.42 (m, 1H), 3.92-3.75 (m, 4H), 2.46-2.41 (m, 1H), 2.22-2.08 (m, 3H).

[1536] Mass (m/e) 382, 384 (M, M+2)

[1537]
PREPARATION 112: Synthesis of 2-bromo-1-[(S)-2-[5-(2-methoxy-1,1-dimethyl-ethyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

150 mg of the title compound was obtained in a yield of 79% in the same manner as in PREPARATION 106, except that 180 mg (0.51 mmol) of (S)-2-[5-(2-methoxy-1,1-diphenyl-ethyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 92, 10 ml of 3N HCl/methyl acetate solution, 53 µl (0.61 mmol) of bromoacetyl bromide and 20 µl (1.12 mmol) of N,N-diisopropylethylamine were used.

$^1$H NMR (CDCl$_3$) δ 5.43-5.39 (m, 1H), 3.91-3.74 (m, 4H), 3.58 (s, 2H), 3.32 (s, 3H), 2.40-2.37 (m, 1H), 2.15-2.06 (m, 3H), 1.47 (s, 6H).

Mass (m/e) 374, 376 (M, M+2)

PREPARATION 113: Synthesis of 2-bromo-1-[(S)-2-(5-cyclopentyl-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

201 mg of the title compound was obtained in a yield of 51% in the same manner as in PREPARATION 106, except that 368 mg (1.10 mmol) of (S)-2-(5-cyclopentyl-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 93, 12 ml of 3N HCl/methyl acetate solution, 120 µl (132 mmol) of bromoacetyl bromide and 420 µl (2.42 mmol) of N,N-diisopropylethylamine were used.

$^1$H NMR (CDCl$_3$) δ 5.40-5.37 (m, 1H), 3.91-3.74 (m, 4H), 3.44-3.40 (m, 1H), 2.43-2.36 (m, 1H), 2.19-1.98 (m, 7H), 1.87-1.83 (m, 2H), 1.74-1.71 (m, 2H).

Mass (m/e) 356, 358 (M, M+2)

PREPARATION 114: Synthesis of 2-bromo-1-[(S)-2-[5-(1-methyl-cyclopentyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

293 mg of the title compound was obtained in a yield of 95% in the same manner as in PREPARATION 106, except that 275 mg (0.86 mmol) of (S)-2-[5-(1-methyl-cyclopentyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 94, 14 ml of 3N HCl/methyl acetate solution, 110 µl (1.28 mmol) of bromoacetyl bromide and 330 µl (1.88 mmol) of N,N-diisopropylethylamine were used.
[1550] $^1$H NMR (CDCl$_3$) $\delta$ 538-530 (m, 1H), 390-373 (m, 4H), 2.42-233 (m, 1H), 2.20-1.96 (m, 3H), 1.60 (s, 3H), 1.55-1.48 (m, 2H), 1.11-1.06 (m, 2H).

[1551] Mass (m/e) 342, 344 (M, M+2)

[1552]

[1553] PREPARATION 115: Synthesis of 2-bromo-1-[(S)-2-(5-adamantyl-1-yl]-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[1554] 364 mg of the title compound was obtained in a yield of 87% in the same manner as in PREPARATION 106, except that 400 mg (1.0 mmol) of (S)-2-(5-adamantane-1-yl]-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 95, 24 ml of 3N HCl/methyl acetate solution, 100 $\mu$l (1.2 mmol) of bromoacetyl bromide and 380 $\mu$l (2.19 mmol) of N,N-diisopropylethylamine were used.

[1555] $^1$H NMR (CDCl$_3$) $\delta$ 5.42-539 (m, 1H), 391-372 (m, 4H), 2.42-234 (m, 1H), 2.16-2.07 (m, 12H), 1.83-1.79 (m, 6H).

[1556] Mass (m/e) 422, 424 (M, M+2)

[1557]

[1558] PREPARATION 116: Synthesis of 2-bromo-1-[(S)-2-[5-(1,1-dimethyl-propyl)]-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[1559] 160 mg of the title compound was obtained in a yield of 58% in the same manner as in PREPARATION 106, except that 260 mg (0.77 mmol) of (S)-2-[5-(1,1-dimethyl-propyl)]-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 96, 15 ml of 3N HCl/methyl acetate solution, 81 $\mu$l (0.93 mmol) of bromoacetyl bromide and 290 $\mu$l (1.69 mmol) of N,N-diisopropylethylamine were used.

[1560] $^1$H NMR (CDCl$_3$) $\delta$ 5.42-530 (m, 1H), 392-374 (m, 4H), 2.44-237 (m, 1H), 2.16-2.04 (m, 3H), 1.82 (q, 2H, J=7.6Hz), 1.44 (s, 6H), 0.84 (t, 3H, J=7.6Hz).

[1561] Mass (m/e) 358, 360 (M, M+2)

[1562]

[1563] PREPARATION 117: Synthesis of 2-bromo-1-[(S)-2-[5-(1-methyl-cyclohexyl)]-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[1564] 313 mg of the title compound was obtained in a yield of 96% in the same manner as in PREPARATION 106, except that 328 mg (0.90 mmol) of
(S)-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 97, 19 ml of 3N HCl/methyl acetate solution, 90 µl (1.10 mmol) of bromoacetyl bromide and 350 µl (1.98 mmol) of N,N-diisopropylethylamine were used.

\[ \text{H NMR (CDCl}_3 \text{) } \delta 5.44-5.40 \text{ (m, 1H), 393-375 (m, 4H), 2.43-2.38 (m, 1H), 2.29-2.24 (m, 2H), 2.16-2.05 (m, 6H), 1.64-1.54 (m, 5H), 1.39 (s, 6H).} \]

Mass (m/e) 384, 386 (M, M+2)

PREPARATION 118: Synthesis of 2-bromo-1-[(S)-2-[5-(2-methoxy-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

176 mg of the title compound was obtained in a yield of 89% in the same manner as in PREPARATION 106, except that 167 mg (0.45 mmol) of (S)-2-[5-(2-methoxy-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 98, 9 ml of 3N HCl/methyl acetate solution, 50 µl (0.54 mmol) of bromoacetyl bromide and 171 µl (0.98 mmol) of N,N-diisopropylethylamine were used.

\[ \text{H NMR (CDCl}_3 \text{) } \delta 816-815 \text{ (m, 1H), 7.60-7.56 (m, 1H), 7.12-7.07 (m, 2H), 5.49-5.45 (m, 1H), 399 (s, 3H), 393-376 (m, 4H), 2.45-2.40 (m, 1H), 2.18-2.10 (m, 3H).} \]

Mass (m/e) 394, 396 (M, M+2)

PREPARATION 119: Synthesis of acetic acid 2-[3-[(S)-1-(2-bromo-acetyl)-pyrrolidine-2-carbonyl]-[1,2,4] oxadiazole-5-yl]-2-methyl-propyl ester

85 mg of the title compound was obtained in a yield of 70% in the same manner as in PREPARATION 106, except that 115 mg (030 mmol) of (S)-2-[5-(2-acetoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 99, 7 ml of 3N HCl/methyl acetate solution, 32 µl (036 mmol) of bromoacetyl bromide and 116 µl (0.66 mmol) of N,N-diisopropylethylamine were used.

\[ \text{H NMR (CDCl}_3 \text{) } \delta 5.41-5.31 \text{ (m, 1H), 430 (s, 3H), 391-375 (m, 4H), 2.43-2.38 (m, 1H), 2.23-2.01 (m, 6H), 1.54 (s, 6H).} \]

Mass (m/e) 402, 404 (M, M+2)
PREPARATION 120: Synthesis of
2-bromo-1-[(2S,4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

98 mg of the title compound was obtained in a yield of 27% in the same manner as in PREPARATION 106, except that 340 mg (1.14 mmol) of (2S,4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 100, 25 ml of 3N HCl/methyl acetate solution, 120 μl (1.36 mmol) of bromoacetyl bromide and 420 μl (2.40 mmol) of N,N-diisopropylethylamine were used.

1H NMR (CDCl3) δ 5.52-5.19 (m, 2H), 4.18-3.97 (m, 2H), 3.95-3.84 (m, 2H), 2.80-2.66 (m, 5H).

Mass (m/e) 320, 322 (M, M+2)

PREPARATION 121: Synthesis of
2-bromo-1-[(2S,4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrroldine-1-yl]-ethanone

140 mg of the title compound was obtained in a yield of 63% in the same manner as in PREPARATION 106, except that 210 mg (0.62 mmol) of (2S,4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 101, 17 ml of 3N HCl/methyl acetate solution, 60 μl (0.27 mmol) of bromoacetyl bromide and 200 μl (1.13 mmol) of N,N-diisopropylethylamine were used.

1H NMR (CDCl3) δ 5.55-5.18 (m, 2H), 4.15-3.96 (m, 2H), 3.95-3.84 (m, 2H), 2.68-2.64 (m, 1H), 2.61-2.56 (m, 1H), 1.51-1.47 (m, 9H).

Mass (m/e) 362, 364 (M, M+2)

PREPARATION 122: Synthesis of
2-bromo-1-[(2S,4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-ethanone

226 mg of the title compound was obtained in a yield of 82% in the same manner as in PREPARATION 106, except that 361 mg (0.73 mmol) of (2S,4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 102, 12 ml of 3N HCl/methyl acetate solution, 100 μl (1.10 mmol) of bromoacetyl bromide and 280 μl (1.61 mmol) of N,N-diisopropylethylamine were used.
[1590] $^1$H NMR (CDCl$_3$) $\delta$ 5.55-5.29 (m, 2H), 4.11-3.76 (m, 4H), 2.68-2.57 (m, 2H), 1.86-1.80 (m, 2H), 1.49-1.43 (m, 6H), 0.88-0.83 (m, 3H).

[1591] Mass (m/e) 376, 378 (M, M+2)

[1592] PREPARATION 123: Synthesis of 2-bromo-1-[(2S,4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[1594] 189 mg of the title compound was obtained in a yield of 76% in the same manner as in PREPARATION 106, except that 237 mg (0.62 mmol) of (2S,4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 103, 12 ml of 3N HCl/methyl acetate solution, 81 $\mu$l (0.93 mmol) of bromoacetyl bromide and 240 $\mu$l (1.37 mmol) of N,N-diisopropylethylamine were used.

[1595] $^1$H NMR (CDCl$_3$) $\delta$ 5.56-530 (m, 2H), 4.12-3.85 (m, 4H), 2.69-2.61 (m, 2H), 2.28-2.25 (m, 2H), 1.65-1.56 (m, 2H), 1.54-1.39 (m, 6H).

[1596] Mass (m/e) 402, 404 (M, M+2)

[1597] PREPARATION 124: Synthesis of 2-bromo-1-[(2S,4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-ethanone

[1599] 106 mg of the title compound was obtained in a yield of 42% in the same manner as in PREPARATION 106, except that 238 mg (0.69 mmol) of (2S,4S)-2-[5-(tert-butyl-[1,2,4]oxadiazole-3-yl)-(1-ethoxy-ethoxy)-methyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester synthesized in PREPARATION 104, 12 ml of 3N HCl/methyl acetate solution, 70 $\mu$l (0.83 mmol) of bromoacetyl bromide and 260 $\mu$l (1.52 mmol) of N,N-diisopropylethylamine were used.

[1600] $^1$H NMR (CDCl$_3$) $\delta$ 5.52-535 (m, 2H), 4.15-395 (m, 2H), 387-380 (m, 2H), 278-270 (m, 1H), 2.29-2.16 (m, 1H), 1.51-1.48 (m, 9H).

[1601] Mass (m/e) 362, 364 (M, M+2)

[1602] EXAMPLE 114: Synthesis of 2-(adamantane-1-ylamino)-1-[2-(3-methyl-[1,2,4]oxadiazole-5-carbonyl)-pyrroolidine-1-yl]-ethanone

[1604] 17 mg (0.056 mmol) of 2-bromo-1-[2S-(3-methyl-[1,2,4] oxadiazole-5-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 105 was
dissolved in 3 ml of dichloromethane. To this were added 31.1 mg (0.23 mmol) of potassium carbonate and 17 mg (0.11 mmol) of 1-adamantaneamine in sequence, followed by stirring for about 15 hours and then isolation and purification by prep-TLC to give 10.1 mg of the title compound in a yield of 48%.

1H NMR (CDCl₃) δ 53-5.4 (1H, m), 3.6-3.8 (2H, m), 3.44 (2H, s), 2.51 (3H, s), 23-24 (1H, m), 2.0-23 (3H, m), 2.1 (3H, br), 1.5-1.7 (12H, m)

Mass (m/e) 373 (M+1)

EXAMPLE 115: Synthesis of 2-(3-hydroxy-adamantane-1-ylamino)-1-[2-(3-methyl-[1,2,4]oxadiazole-5-carbonyl)-pyrrolidine-1-yl]-ethanone

88 mg of the title compound was obtained in a yield of 53% in the same manner as in EXAMPLE 114, except that 129 mg (0.043 mmol) of 2-bromo-1-[2S-(3-methyl-[1,2,4]oxadiazole-5-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 105, 23.6 mg (0.17 mmol) of potassium carbonate and 14.4 mg (0.085 mmol) of 3-hydroxy-1-adamantaneamine were used.

1H NMR (CDCl₃) δ 53-5.4 (1H, m), 3.6-3.8 (2H, m), 3.45 (2H, s), 2.51 (3H, s), 23-24 (1H, m), 2.26 (2H, br), 2.0-22 (3H, m), 1.5-1.7 (12H, m)

Mass (m/e) 389 (M+1)

EXAMPLE 116: Synthesis of 2-(adamantane-1-ylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

25.7 mg of the title compound was obtained in a yield of 91% in the same manner as in EXAMPLE 114, except that 230 mg (0.076 mmol) of 2-bromo-1-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106, 420 mg (0.30 mmol) of potassium carbonate and 23.0 mg (0.15 mmol) of 1-adamantaneamine were used.

1H NMR (CDCl₃) δ 53-5.4 (1H, m), 3.6-3.8 (2H, m), 3.44 (2H, s), 2.67 (3H, s), 23-24(H, m), 2.0-23 (3H, m), 2.1 (3H, br s), 1.5-1.8 (12H, m)

Mass (m/e) 373 (M+1)

EXAMPLE 117: Synthesis of 2-tert-butilamino-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

163 mg of the title compound was obtained in a yield of 66% in the same manner
as in EXAMPLE 114, except that 25.5 mg (0.084 mmol) of
2-bromo-1-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
synthesized in PREPARATION 106, 46.7 mg (0.034 mmol) of potassium carbonate and
123 mg (0.17 mmol) of tert-butyamine were used.

\[1620\] \(^{1}\text{H NMR (CDCl}_3\) \(\delta\) 53.5-5.4 (1H, m), 3.6-3.8 (2H, m), 3.41 (2H, s), 2.67 (3H, s),
23-24 (1H, m), 20-23 (3H, m), 1.09 (9H, s)

[1621] Mass (m/e) 295 (M+1)

[1622]

[1623] EXAMPLE 118: Synthesis of
2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-[2-(5-methyl-[1,2,4]oxadiazole-
3-carbonyl)-pyrrolidine-1-yl]-ethanone

[1624] 12.0 mg of the title compound was obtained in a yield of 72% in the same manner
as in EXAMPLE 114, except that 12.9 mg (0.043 mmol) of
2-bromo-1-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
synthesized in PREPARATION 106, 23.6 mg (0.017 mmol) of potassium carbonate and
143 mg (0.085 mmol) of 2-(4-fluorophenyl)-1,1-dimethyl-ethylamine were used.

[1625] \(^{1}\text{H NMR (CDCl}_3\) \(\delta\) 7.1-7.2 (2H, m), 6.9-7.0 (2H, m), 53.5-5.4 (1H, m), 37 (1H, m),
37-36 (1H, m), 346 (2H, s), 267 (3H, s), 27-26 (1H, m), 23-24 (1H, m), 20-23
(3H, m), 1.04 (3H, s), 1.02 (3H, s)

[1626] Mass (m/e) 389 (M+1)

[1627]

[1628] EXAMPLE 119: Synthesis of 2-(2-hydroxy-1,1-dimethyl-ethylamino) -
1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

[1629] 7.4 mg of the title compound was obtained in a yield of 52% in the same manner as
in EXAMPLE 114, except that 137 mg (0.045 mmol) of
2-bromo-1-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
synthesized in PREPARATION 106, 25.0 mg (0.018 mmol) of potassium carbonate and
81 mg (0.091 mmol) of 2-hydroxy-1,1-dimethyl-ethylamine were used.

[1630] \(^{1}\text{H NMR (CDCl}_3\) \(\delta\) 53.5-5.4 (1H, m), 3.6-3.8 (2H, m), 33-34 (2H, m), 318 (2H, s),
2.68 (3H, s), 23-24 (1H, m), 20-23 (3H, m), 1.05 (6H, s)

[1631] Mass (m/e) 311 (M+1)

[1632]

[1633] EXAMPLE 120: Synthesis of
2-(1-benzyl-2-hydroxy-1-methyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
[1634] 10.9 mg of the title compound was obtained in a yield of 60% in the same manner as in EXAMPLE 114, except that 14.2 mg (0.047 mmol) of 2-bromo-1-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106, 32.5 mg (0.24 mmol) of potassium carbonate and 19.0 mg (0.094 mmol) of 1-benzyl-2-hydroxy-1-methyl-ethylamine hydrochloride salt were used.

[1635] $^1$H NMR (CDCl$_3$) $\delta$ 7.2-7.4 (5H, m), 53-5.4 (1H, m), 36-38 (2H, m), 3.4-3.5 (2H, m), 3.1-3.3 (2H, m), 2.5-2.8 (2H, m), 2.68 (3H, s), 23-2.4 (1H, m), 2.0-23 (3H, m), 0.92 (3H, s)

[1636] Mass (m/e) 387 (M+1)

[1637]

[1638] **EXAMPLE 121: Synthesis of 2-[(2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino)-1-[[2-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone**

[1639] 4.7 mg of the title compound was obtained in a yield of 24% in the same manner as in EXAMPLE 114, except that 87 mg (0.030 mmol) of 2-bromo-1-[2S-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 107, 16.7 mg (0.12 mmol) of potassium carbonate and 10.1 mg (0.060 mmol) of 2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamine were used.

[1640] $^1$H NMR (CDCl$_3$) $\delta$ 8.85 (1H, s), 7.1-7.2 (2H, m), 6.9-7.0 (2H, m), 53-5.4 (1H, m), 36-38 (2H, m), 348 (2H, s), 2.65 (2H, ABq, J=12Hz), 23-2.4 (1H, m), 2.0-23 (3H, m), 1.05 (3H, s), 1.03 (3H, s)

[1641] Mass (m/e) 375 (M+1)

[1642]

[1643] **EXAMPLE 122: Synthesis of 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[(2-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone**

[1644] 6.0 mg of the title compound was obtained in a yield of 0.9% in the same manner as in EXAMPLE 114, except that 61.7 mg (0.21 mmol) of 2-bromo-1-[2S-[[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 107, 118 mg (0.86 mmol) of potassium carbonate and 382 mg (0.43 mmol) of 2-hydroxy-1,1-dimethyl-ethylamine were used.

[1645] $^1$H NMR (CDCl$_3$) $\delta$ 8.88 (1H, s), 53-5.4 (1H, m), 36-38 (2H, m), 344 (2H, m), 3.2 (2H, m), 23-2.4 (1H, m), 2.0-23 (3H, m), 1.06 (3H, s), 1.04 (3H, s)

[1646] Mass (m/e) 297 (M+1)
EXAMPLE 123: Synthesis of 1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

5.2 mg of the title compound was obtained in a yield of 68% in the same manner as in EXAMPLE 114, except that 7.5 mg (0.022 mmol) of 2-bromo-[2S-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106, 12.2 mg (0.09 mmol) of potassium carbonate and 39 mg (0.044 mmol) of 2-hydroxy-1,1-dimethyl-ethylamine were used.

\(^1\)H NMR (CDCl) \(\delta\) 53-5.4 (1H, m), 3.6-3.8 (2H, m), 3.4 (2H, ABq, J=16Hz), 3.18 (2H, m), 2.3-2.4 (1H, m), 2.0-2.3 (3H, m), 1.48 (9H, s), 1.05 (6H, s)

Mass (m/e) 353 (M+1)

EXAMPLE 124: Synthesis of 1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-[2-(4-fluorophenyl)-1,1-dimethyl-ethylamino]-ethanone

53 mg of the title compound was obtained in a yield of 78% in the same manner as in EXAMPLE 114, except that 5.4 mg (0.016 mmol) of 2-bromo-[2S-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106, 87 mg (0.063 mmol) of potassium carbonate and 5.2 mg (0.031 mmol) of 2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamine were used.

\(^1\)H NMR (CDCl) \(\delta\) 7.1-7.2 (2H, m), 6.9-7.0 (2H, m), 5.4-5.5 (1H, m), 3.6-3.8 (2H, m), 3.47 (2H, s), 2.65 (2H, ABq, J=12Hz), 2.23-2.4 (1H, m), 2.0-2.3 (3H, m), 1.48 (9H, s), 1.04 (3H, s), 1.03 (3H, s)

Mass (m/e) 431 (M+1)

EXAMPLE 125: Synthesis of 2-tert-butyl-1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

3.8 mg of the title compound was obtained in a yield of 59% in the same manner as in EXAMPLE 114, except that 6.5 mg (0.019 mmol) of 2-bromo-[2S-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106, 10.5 mg (0.076 mmol) of potassium carbonate and 2.8 mg (0.038 mmol) of tert-butylamine were used.

\(^1\)H NMR (CDCl) \(\delta\) 53-5.4 (1H, m), 3.6-3.8 (2H, m), 3.42 (2H, m), 2.3-2.4 (1H, m), 2.0-2.3 (3H, m), 1.47 (9H, m), 1.09 (9H, s)

Mass (m/e) 337 (M+1)
EXAMPLE 126: Synthesis of 2-tert-butyl-1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

5.0 mg of the title compound was obtained in a yield of 77% in the same manner as in EXAMPLE 114, except that 6.6 mg (0.021 mmol) of 2-bromo-1-[(S)-2-(5-ethyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 109, 31 mg (0.042 mmol) of tert-butylamine and 11.5 mg (0.084 mmol) of potassium carbonate were used.

$^1$H NMR (CDCl$_3$) $\delta$ 5.42-5.39 (m, 1H), 3.78-3.72 (m, 1H), 3.64-3.62 (m, 1H), 3.51-3.37 (m, 2H), 3.01 (q, 2H, J=7.6Hz), 2.39-2.32 (m, 1H), 2.17-2.01 (m, 3H), 1.46 (t, 3H, J=7.6Hz), 1.13 (s, 3H).

Mass (m/e) 309 (M+1)

EXAMPLE 127: Synthesis of 1-[2-(5-ethyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

3.5 mg of the title compound was obtained in a yield of 45% in the same manner as in EXAMPLE 114, except that 7.7 mg (0.024 mmol) of 2-bromo-1-[(S)-2-(5-ethyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 109, 43 mg (0.049 mmol) of 2-hydroxy-1,1-dimethyl-methylamine and 13.5 mg (0.097 mmol) of potassium carbonate were used.

$^1$H NMR (CDCl$_3$) $\delta$ 5.40-5.37 (m, 1H), 3.73-3.70 (m, 1H), 3.58-3.56 (m, 1H), 3.43-3.41 (m, 2H), 3.18 (s, 2H), 3.03-2.98 (m, 2H), 2.40-2.35 (m, 1H), 2.14-2.02 (m, 5H), 1.47-1.42 (m, 3H), 1.05 (s, 6H).

Mass (m/e) 325 (M+1)

EXAMPLE 128: Synthesis of 1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(cyclohexyl-2-hydroxy-1,1-dimethyl-ethylamino )-ethanone

2.6 mg of the title compound was obtained in a yield of 28% in the same manner as in EXAMPLE 114, except that 7.4 mg (0.022 mmol) of 2-bromo-1-[(S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 108, 89 mg (0.043 mmol) of 2-amino-1-cyclohexyl-2-methyl-propane-1-ol and 11.8 mg (0.172 mmol) of potassium carbonate were used.
[1675] $^1$H NMR (CDCl$_3$) $\delta$ 5.45-5.34 (m, 1H), 3.75-3.67 (m, 1H), 3.61-3.54 (m, 1H), 3.46 (s, 2H), 3.10-3.03 (m, 1H), 2.65-2.00 (br s, 1H), 2.41-2.34 (m, 1H), 2.13-2.05 (m, 3H), 1.51-1.43 (m, 9H), 1.30-1.07 (m, 11H).

[1676] Mass (m/e) 435 (M+1)

[1677]

[1678] **EXAMPLE 129:** Synthesis of 1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone

[1679] 4.4 mg of the title compound was obtained in a yield of 59% in the same manner as in EXAMPLE 114, except that 6.0 mg (0.017 mmol) of 2-bromo-1-[(S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 108, 7.0 mg (0.035 mmol) of 2-amino-2-methyl-1-phenyl-propane-1-ol and 9.6 mg (0.068 mmol) of potassium carbonate were used.

[1680] $^1$H NMR (CDCl$_3$) $\delta$ 7.36-7.24 (m, 5H), 5.46-5.34 (m, 1H), 4.42-3.61 (m, 2H), 3.77-3.71 (m, 1H), 3.63-3.47 (m, 1H), 2.38-2.35 (m, 1H), 2.17-2.01 (m, 4H), 2.20-1.70 (br s, 1H), 1.51-1.46 (m, 9H), 1.04-0.87 (m, 6H).

[1681] Mass (m/e) 429 (M+1)

[1682]

[1683] **EXAMPLE 130:** Synthesis of 1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamine)-ethanone

[1684] 5.1 mg of the title compound was obtained in a yield of 50% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.029 mmol) of 2-bromo-1-[(S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 108, 7.2 mg (0.058 mmol) of 2-amino-2-methyl-1-phenyl-propane-1-ol and 16.0 mg (0.116 mmol) of potassium carbonate were used.

[1685] $^1$H NMR (CDCl$_3$) $\delta$ 5.34-5.30 (m, 1H), 4.49-4.10 (m, 2H), 3.92-3.84 (m, 1H), 3.76-3.49 (m, 2H), 2.07-1.95 (m, 1H), 1.83-1.57 (m, 4H), 1.51-1.41 (m, 9H), 1.31-1.26 (m, 2H), 0.65-0.61 (m, 1H), 0.52-0.48 (m, 1H), 0.43-0.39 (m, 2H).

[1686] Mass (m/e) 351 (M+1)

[1687]

[1688] **EXAMPLE 131:** Synthesis of 2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
[1689] 81 mg of the title compound was obtained in a yield of 59% in the same manner as in EXAMPLE 114, except that 11.0 mg (0.036 mmol) of 2-bromo-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106, 14.0 mg (0.073 mmol) of 2-cyclohexyl-1,1-dimethyl-methylamine and 20.1 mg (0.146 mmol) of potassium carbonate were used.

[1690] $^1$H NMR (CDCl$_3$) $\delta$ 538-535 (m, 1H), 372-368 (m, 1H), 361-359 (m, 1H), 345-338 (m, 2H), 367 (s, 3H), 235-225 (m, 1H), 2.14-2.03 (m, 4H), 1.72-1.61 (m, 5H), 1.35-1.23 (m, 5H), 1.10-1.05 (m, 7H), 0.97-0.89 (m, 2H).

[1691] Mass (m/e) 377 (M+1)

[1692] [1690]

[1693] EXAMPLE 132: Synthesis of 1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone

[1694] 6.1 mg of the title compound was obtained in a yield of 50% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.029 mmol) of 2-bromo-1-[(S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 108, 11.1 mg (0.058 mmol) of 2-cyclohexyl-1,1-dimethyl-methylamine and 160 mg (0.116 mmol) of potassium carbonate were used.

[1695] $^1$H NMR (CDCl$_3$) $\delta$ 5.42-5.39 (m, 1H), 375-371 (m, 1H), 361-357 (m, 1H), 348-318 (m, 2H), 237-231 (m, 1H), 2.15-2.00 (m, 4H), 1.73-1.62 (m, 5H), 1.50-1.46 (m, 9H), 1.31-1.20 (m, 6H), 1.13-1.06 (m, 6H), 0.98-0.88 (m, 2H).

[1696] Mass (m/e) 419 (M+1)

[1697] [1694]

[1698] EXAMPLE 133: Synthesis of 2-methyl-2-[2-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(oxo-ethylamino)-propionic acid tert-butyl ester

[1699] 60 mg of the title compound was obtained in a yield of 47% in the same manner as in EXAMPLE 114, except that 102 mg (0.307 mmol) of 2-bromo-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106, 107.5 mg (0.675 mmol) of 2-amino-2-methyl-propionic acid tert-butyl ester and 186 mg (1.35 mmol) of potassium carbonate were used.

[1700] $^1$H NMR (CDCl$_3$) $\delta$ 538-535 (m, 1H), 367-363 (m, 1H), 356-353 (m, 1H), 344-330 (m, 2H), 2.67 (s, 3H), 233-230 (m, 1H), 2.14-2.00 (m, 4H), 1.48-1.40 (m, 9H), 1.28 (s, 6H).
EXAMPLE 134: Synthesis of 2-tert-butylamino-1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

5.5 mg of the title compound was obtained in a yield of 54% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.031 mmol) of 2-bromo-1-[(S)-2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 110, 4.6 mg (0.063 mmol) of tert-butylamine and 17.4 mg (0.126 mmol) of potassium carbonate were used.

\[^{1}H\text{ NMR (CDCl}_3\text{)}\delta 5.40-5.36\text{ (m, 1H), 3.74-3.71 (m, 1H), 3.65-3.59 (m, 1H), 3.52-3.42 (m, 2H), 2.40-2.27 (m, 2H), 2.14-2.00 (m, 4H), 1.37-1.29 (m, 4H), 1.13 (s, 9H). Mass (m/e) 321 (M+1)\]

EXAMPLE 135: Synthesis of 1-[2-(5-cyclopropyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

2.8 mg of the title compound was obtained in a yield of 23% in the same manner as in EXAMPLE 114, except that 11.5 mg (0.036 mmol) of 2-bromo-1-[(S)-2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 110, 6.5 mg (0.072 mmol) of 2-hydroxy-1,1-dimethyl-methylamine and 20.0 mg (0.144 mmol) of potassium carbonate were used.

\[^{1}H\text{ NMR (CDCl}_3\text{)}\delta 5.38-5.30\text{ (m, 1H), 3.71-3.67 (m, 1H), 3.57-3.55 (m, 1H), 3.53-3.39 (m, 2H), 3.22-3.16 (m, 2H), 2.35-2.26 (m, 1H), 2.13-1.90 (m, 6H), 1.36-1.28 (m, 4H), 1.06 (s, 6H).\]

Mass (m/e) 337 (M+1)

EXAMPLE 136: Synthesis of 2-methyl-2-[2-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(oxo-ethylamino)-propionic acid trifluorooacetate

12.0 mg (0.032 mmol) of 2-methyl-2-[2-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(oxo-ethylamino)-propionic acid tert-butyl ester was dissolved in 3 ml of methylene chloride, and 1.5 ml of trifluoroacetic acid was slowly added dropwise thereto at room temperature. After stirring at room temperature for 2 hours, the solvent and trifluoroacetic acid were removed under reduced pressure. The
residue was isolated and purified by Prep-TLC to give 85 mg of the title compound in a yield of 62%.

[1714] ³¹H NMR (CDCl₃) δ 5.40-5.37 (m, 1H), 4.93 (br s, 3H), 4.12 (br s, 1H), 3.75-3.70 (m, 2H), 3.36-3.33 (m, 4H), 2.72-2.64 (m, 4H), 2.46-2.43 (m, 1H), 2.12-2.10 (m, 2H), 1.63 (br s, 4H). ms 325 (M+1)

[1715]

[1716] EXAMPLE 137: Synthesis of 1-[(4S)-2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone

[1717] 5.9 mg of the title compound was obtained in a yield of 48% in the same manner as in EXAMPLE 114, except that 9.0 mg (0.025 mmol) of 2-bromo-1-[(2S,4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 121, 9.5 mg (0.050 mmol) of 2-cyclohexyl-1,1-dimethyl-methylamine and 137 mg (0.099 mmol) of potassium carbonate were used.

[1718] ³¹H NMR (CDCl₃) δ 5.55-5.33 (m, 2H), 4.09-3.89 (m, 2H), 3.50-3.31 (m, 2H), 2.80-2.63 (m, 1H), 2.20-1.80 (m, 2H), 2.71-1.62 (m, 4H), 1.51-1.45 (m, 9H), 1.34-1.23 (m, 6H), 1.13-0.88 (m, 8H).

[1719] Mass (m/e) 437 (M+1)

[1720]

[1721] EXAMPLE 138: Synthesis of 2-(1-hydroxymethyl-cyclopentylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

[1722] 5.9 mg of the title compound was obtained in a yield of 48% in the same manner as in EXAMPLE 114, except that 11.0 mg (0.036 mmol) of 2-bromo-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106, 9.0 mg (0.073 mmol) of 1-amino-1-cyclopentane ethanol and 18 mg (0.146 mmol) of potassium carbonate were used.

[1723] ³¹H NMR (CDCl₃) δ 5.39-5.35 (m, 1H), 3.73-3.67 (m, 1H), 3.64-3.53 (m, 1H), 3.43 (s, 2H), 3.26-3.20 (m, 1H), 2.69 (s, 3H), 2.43-2.32 (m, 2H), 2.17-1.99 (m, 4H), 1.73-1.68 (m, 2H), 1.60-1.46 (m, 6H).

[1724] Mass (m/e) 337 (M+1)

[1725]

[1726] EXAMPLE 139: Synthesis of 1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
[1727] 2.6 mg of the title compound was obtained in a yield of 26% in the same manner as in EXAMPLE 114, except that 9.0 mg (0.026 mmol) of 2-bromo-1-[(S)-2-(5-tert-butyl-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethane synthesized in PREPARATION 108, 80 mg (0.052 mmol) of 1-amino-1-cyclopentane ethanol and 14.4 mg (0.104 mmol) of potassium carbonate were used.

[1728] 'H NMR (CDCl₃) δ 5.42-5.39 (m, 1H), 3.72-3.68 (m, 1H), 3.58-3.53 (m, 1H), 3.44 (s, 2H), 3.27-3.21 (m, 2H), 2.41-2.32 (m, 1H), 2.15-1.99 (m, 5H), 1.74-1.69 (m, 2H), 1.64-1.44 (m, 15H).

[1729] Mass (m/e) 379 (M+1)

[1730]

[1731] **EXAMPLE 140: Synthesis of 1-{2-[5-(2-methoxy-1,1-dimethyl-ethyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl}-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone**

[1732] 19.0 mg of the title compound was obtained in a yield of 46% in the same manner as in EXAMPLE 114, except that 45 mg (0.112 mmol) of acetic acid 2-{3-[S]-1-(2-bromo-acetyl)-pyrrolidine-2-carbonyl}-1,2,4]oxadiazole-5-yl}-2-methyl-1-propyl ester synthesized in PREPARATION 119 and 202 mg (0.224 mmol) of 2-hydroxy-1,1-dimethyl-methylamine were used.

[1733] 'H NMR (CDCl₃) δ 5.41-5.38 (m, 1H), 4.30 (s, 2H), 3.75-3.69 (m, 1H), 3.60-3.54 (m, 1H), 3.48-3.33 (m, 2H), 3.19 (s, 2H), 2.50-2.33 (m, 1H), 2.16-2.06 (m, 3H), 2.04 (s, 3H), 1.51 (s, 6H), 1.06 (s, 6H).

[1734] Mass (m/e) 412 (M+1)

[1735]

[1736] **EXAMPLE 141: Synthesis of 2-tert-butylamino-1-{2-[5-(2-methoxy-1,1-dimethyl-ethyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl}-ethanone**

[1737] 53 mg of the title compound was obtained in a yield of 55% in the same manner as in EXAMPLE 114, except that 9.5 mg (0.024 mmol) of acetic acid 2-{3-[S]-1-(2-bromo-acetyl)-pyrrolidine-2-carbonyl}-1,2,4]oxadiazole-5-yl}-2-methyl-1-propyl ester synthesized in PREPARATION 119, 5.2 mg (0.071 mmol) of tert-butylamine and 33 mg (0.024 mmol) of potassium carbonate were used.

[1738] 'H NMR (CDCl₃) δ 5.42-5.39 (m, 1H), 4.31-4.30 (m, 2H), 3.77-3.69 (m, 1H), 3.64-3.58 (m, 1H), 3.49-3.36 (m, 2H), 2.40-2.32 (m, 1H), 2.17-2.02 (m, 7H), 1.50 (s, 6H), 1.11 (s, 9H).
[1739] Mass (m/e) 395 (M+1)

[1740]

[1741] EXAMPLE 142: Synthesis of 1-{2-[5-(2-methoxy-1,1-dimethyl-ethyl)-1,2,4]oxadiazole-3-carbonyl}-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[1742] 39 mg of the title compound was obtained in a yield of 36% in the same manner as in EXAMPLE 114, except that 11.0 mg (0.027 mmol) of acetic acid 2-{3-[(S)-1-(2-bromo-acetyl)-pyrroldine-2-carbonyl]-1,2,4]oxadiazole-5-yl}-2-methyl-propyl ester synthesized in PREPARATION 119, 9.4 mg (0.224 mmol) of 1-amino-1-cyclopentane ethanol and 3.8 mg (0.027 mmol) of potassium carbonate were used.

[1743] $^1$H NMR (CDCl$_3$) $\delta$ 5.42-5.38 (m, 1H), 4.30 (s, 2H), 3.73-3.68 (m, 1H), 3.59-3.53 (m, 1H), 3.43 (s, 2H), 3.23 (s, 2H), 2.41-2.31 (m, 1H), 2.14-2.06 (m, 3H), 2.04 (s, 3H), 1.73-1.70 (m, 2H), 1.60-1.51 (m, 14H).

[1744] Mass (m/e) 437 (M+1)

[1745]

[1746] EXAMPLE 143: Synthesis of 1-{2-[5-(1,1-dimethyl-propyl)-1,2,4]oxadiazole-3-carbonyl}-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[1747] 53 mg of the title compound was obtained in a yield of 55% in the same manner as in EXAMPLE 114, except that 9.5 mg (0.027 mmol) of 2-bromo-1-[(S)-2-[5-(1,1-dimethyl-propyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 116, 7.1 mg (0.080 mmol) of 2-hydroxy-1,1-dimethyl-methamine and 73 mg (0.053 mmol) of potassium carbonate were used.

[1748] $^1$H NMR (CDCl$_3$) $\delta$ 5.44-5.40 (m, 1H), 4.20-3.80 (br s, 2H), 3.75-3.72 (m, 2H), 3.65-3.55 (m, 2H), 3.42-3.33 (m, 2H), 2.45-2.36 (m, 1H), 2.15-2.02 (m, 3H), 1.83 (q, 2H, J=7.6Hz), 1.45 (s, 6H), 1.17 (s, 6H), 0.85 (t, 3H, J=7.6Hz).

[1749] Mass (m/e) 367 (M+1)

[1750]

[1751] EXAMPLE 144: Synthesis of 2-tert-buty1-1-{2-[5-(1,1-dimethyl-propyl)-1,2,4]oxadiazole-3-carbonyl}-pyrrolidine-1-yl]-ethanone

[1752] 2.8 mg of the title compound was obtained in a yield of 23% in the same manner as in EXAMPLE 114, except that 9.5 mg (0.027 mmol) of
2-bromo-1-\{(S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl\}-ethane synthesized in PREPARATION 116, 5.8 mg (0.080 mmol) of tert-butylamine and 73 mg (0.053 mmol) of potassium carbonate were used.

\[\text{1H NMR (CDCl}_3\text{) } \delta 5.42-5.39 \text{ (m, 1H), 3.74-3.70 (m, 1H), 3.61-3.59 (m, 1H), 3.49-3.35 (m, 2H), 2.40-2.28 (m, 1H), 2.13-2.03 (m, 3H), 2.00-1.90 (br s, 1H), 1.82 (q, 2H, J=7.6Hz), 1.47-1.44 (m, 6H), 1.10 (s, 9H), 0.84 (t, 3H, J=7.6Hz)\]

Mass (m/e) 351 (M+1)

EXAMPLE 145: Synthesis of 1-\{2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl\}-2-(1-hydroxymethyl-cyclopentylamino)-ethane

7.1 mg of the title compound was obtained in a yield of 68% in the same manner as in EXAMPLE 114, except that 9.5 mg (0.027 mmol) of 2-bromo-1-\{(S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl\}-ethane synthesized in PREPARATION 116, 9.2 mg (0.080 mmol) of 1-amino-1-cyclopentane ethanol and 73 mg (0.053 mmol) of potassium carbonate were used.

\[\text{1H NMR (CDCl}_3\text{) } \delta 5.42-5.39 \text{ (m, 1H), 3.78-3.67 (m, 1H), 3.60-3.53 (m, 1H), 3.48-3.38 (m, 2H), 3.26-3.20 (m, 2H), 2.39-2.32 (m, 1H), 2.13-2.02 (m, 3H), 1.82 (q, 2H, J=7.6Hz), 1.78-1.65 (br s, 2H), 1.62-1.40 (m, 13H), 0.85 (t, 3H, J=7.6Hz)\]

Mass (m/e) 393 (M+1)

EXAMPLE 146: Synthesis of 2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethane

4.9 mg of the title compound was obtained in a yield of 39% in the same manner as in EXAMPLE 114, except that 10.8 mg (0.036 mmol) of 2-bromo-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethane synthesized in PREPARATION 106, 143 mg (0.107 mmol) of 2-methoxymethoxy-1,1-dimethyl-ethylamine and 9.9 mg (0.071 mmol) of potassium carbonate were used.

\[\text{1H NMR (CDCl}_3\text{) } \delta 5.38-5.35 \text{ (m, 1H), 4.61 (s, 2H), 3.73-3.68 (m, 1H), 3.62-3.56 (m, 1H), 3.49-3.41 (m, 2H), 3.38-3.28 (m, 5H), 2.67 (s, 3H), 2.35-2.28 (m, 1H), 2.14-1.98 (m, 4H), 1.90 (br s, 1H), 1.25 (s, 6H)\]

Mass (m/e) 355 (M+1)
EXAMPLE 147: Synthesis of
2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
7.0 mg of the title compound was obtained in a yield of 47% in the same manner as in EXAMPLE 114, except that 14.0 mg (0.046 mmol) of 2-bromo-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106, 10.0 mg (0.140 mmol) of 2-methoxy-1,1-dimethyl-ethylamine and 12.8 mg (0.093 mmol) of potassium carbonate were used.

^1H NMR (CDCl$_3$) $\delta$ 5.38-5.25 (m, 1H), 3.72-3.68 (m, 1H), 3.61-3.58 (m, 1H), 3.45-3.44 (m, 2H), 3.32 (s, 3H), 3.18 (s, 2H), 2.67 (s, 3H), 2.35-2.30 (m, 1H), 2.15-2.00 (m, 4H), 1.06 (s, 6H).

Mass (m/e) 325 (M+1)

EXAMPLE 148: Synthesis of
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
5.0 mg of the title compound was obtained in a yield of 41% in the same manner as in EXAMPLE 114, except that 12.0 mg (0.032 mmol) of 2-bromo-1-{(S)-2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl}-ethanonesynthesized in PREPARATION 112, 86 mg (0.096 mmol) of 2-hydroxy-1,1-dimethyl-methylamine and 89 mg (0.064 mmol) of potassium carbonate were used.

^1H NMR (CDCl$_3$) $\delta$ 5.42-5.39 (m, 1H), 3.73-3.69 (m, 1H), 3.60-3.55 (m, 1H), 3.48-3.38 (m, 2H), 3.33-3.32 (m, 3H), 3.19 (s, 2H), 2.37-2.34 (m, 2H), 2.13-2.05 (m, 4H), 1.49-1.47 (m, 6H), 1.06 (s, 6H).

Mass (m/e) 383 (M+1)

EXAMPLE 149: Synthesis of
2-tert-butyramino-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
43 mg of the title compound was obtained in a yield of 38% in the same manner as in EXAMPLE 114, except that 11.7 mg (0.032 mmol) of 2-bromo-1-{(S)-2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl}-p
yrrolidine-1-yl]-ethanonesynthesized in PREPARATION 112, 6.9 mg (0.094 mmol) of tert-butylamine and 87 mg (0.063 mmol) of potassium carbonate were used.

\[ 1^1H \text{ NMR (CDCl}_3\text{)} \delta 5.42-5.37 (m, 1H), 374-370 (m, 1H), 361-357 (m, 3H), 343 (s, 2H), 332-328 (m, 3H), 340-330 (m, 1H), 2.13-2.03 (m, 3H), 1.88 (br s, 1H), 1.51-1.46 (m, 6H), 1.10 (s, 9H). \]

Mass (m/e) 367 (M+1)

EXAMPLE 150: Synthesis of 2-(1-hydroxymethyl-cyclopentylamino)-1-(2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

12.4 mg of the title compound was obtained in a yield of 67% in the same manner as in EXAMPLE 114, except that 17.0 mg (0.045 mmol) of 2-bromo-1-[(S)-2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 112, 16.0 mg (0.136 mmol) of 1-amino-1-cyclopentane ethanol and 130 mg (0.098 mmol) of potassium carbonate were used.

\[ 1^1H \text{ NMR (CDCl}_3\text{)} \delta 5.42-5.39 (m, 1H), 370-365 (m, 1H), 358-355 (m, 3H), 342 (s, 2H), 330 (s, 3H), 324 (s, 3H), 2.40-2.35 (m, 1H), 2.12-2.03 (m, 4H), 2.00 (br s, 1H), 1.72-1.71 (m, 2H), 1.60-1.43 (m, 12H). \]

Mass (m/e) 409 (M+1)

EXAMPLE 151: Synthesis of 1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

4.0 mg of the title compound was obtained in a yield of 17% in the same manner as in EXAMPLE 114, except that 21.0 mg (0.056 mmol) of 2-bromo-1-[(S)-2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 112, 224 mg (0.168 mmol) of 2-methoxymethoxy-1,1-dimethyl-ethylamine and 15.5 mg (0.112 mmol) of potassium carbonate were used.

\[ 1^1H \text{ NMR (CDCl}_3\text{)} \delta 5.43-5.40 (m, 1H), 4.62-4.54 (m, 2H), 375-370 (m, 1H), 360-356 (m, 3H), 345 (s, 2H), 338-330 (m, 8H), 2.40-2.15 (m, 2H), 2.12-2.02 (m, 3H), 1.51-1.46 (m, 6H), 1.09 (m, 6H). \]

Mass (m/e) 427 (M+1)
EXAMPLE 152: Synthesis of
2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)\[1,2,4\]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

7.7 mg of the title compound was obtained in a yield of 48% in the same manner as in EXAMPLE 114, except that 15.0 mg (0.040 mmol) of 2-bromo-1-\((S)-2-(5-(2-methoxy-1,1-dimethyl-ethyl)\[1,2,4\]oxadiazole-3-carbonyl]-pyrrolidine-1-yl\]-ethanone was synthesized in PREPARATION 112, 124 mg (0.120 mmol) of 2-methoxy-1,1-dimethyl-ethylamine and 11.1 mg (0.108 mmol) of potassium carbonate were used.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.45-5.42 (m, 1H), 3.77-3.71 (m, 1H), 3.63-3.59 (m, 3H), 3.49-3.48 (m, 2H), 3.35-3.34 (m, 2H), 3.30-3.21 (m, 2H), 2.40-2.30 (m, 1H), 2.15-1.90 (m, 4H), 1.54-1.49 (m, 6H), 1.10 (s, 6H).

Mass (m/e) 397 (M+1)

EXAMPLE 153: Synthesis of 1-[2-(5-cyclopentyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

5.8 mg of the title compound was obtained in a yield of 49% in the same manner as in EXAMPLE 114, except that 11.5 mg (0.032 mmol) of 2-bromo-1-\((S)-2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl\]-ethanone was synthesized in PREPARATION 113, 86 mg (0.097 mmol) of 2-hydroxy-1,1-dimethyl-methylamine and 89 mg (0.065 mmol) of potassium carbonate were used.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.41-5.38 (m, 1H), 3.75-3.70 (m, 1H), 3.63-3.50 (m, 1H), 3.44-3.40 (m, 3H), 3.20-3.18 (m, 2H), 2.40-2.30 (m, 1H), 2.18-1.98 (m, 8H), 1.90-1.85 (m, 2H), 1.74-1.71 (m, 2H), 1.05 (s, 6H).

Mass (m/e) 365 (M+1)

EXAMPLE 154: Synthesis of 2-tert-butylamino-1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

6.0 mg of the title compound was obtained in a yield of 61% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.028 mmol) of 2-bromo-1-\((S)-2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl\]-ethanone was synthesized in PREPARATION 113, 6.2 mg (0.084 mmol) of tert-butylamine and 7.8 mg (0.056 mmol) of potassium carbonate were used.
[1803] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.41-5.37 (m, 1H), 3.77-3.70 (m, 1H), 3.65-3.55 (m, 1H), 3.46-3.39 (m, 3H), 2.35-1.98 (m, 8H), 1.86-1.82 (m, 2H), 1.73-1.70 (m, 2H), 1.11 (s, 9H).

[1804] Mass (m/e) 349 (M+1)

[1805]

[1806] EXAMPLE 155: Synthesis of 1-[2-(5-cyclopentyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)ethanone

[1807] 7.5 mg of the title compound was obtained in a yield of 65% in the same manner as in EXAMPLE 114, except that 10.5 mg (0.030 mmol) of 2-bromo-1-[(S)-2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone was synthesized in PREPARATION 113, 10.2 mg (0.088 mmol) of 1-amino-1-cyclopentane ethanol and 82 mg (0.059 mmol) of potassium carbonate were used.

[1808] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.41-5.38 (m, 1H), 3.73-3.67 (m, 1H), 3.58-3.52 (m, 1H), 3.46-3.38 (m, 3H), 3.27-3.20 (m, 2H), 2.38-2.33 (m, 1H), 2.18-1.77 (m, 8H), 1.87-1.83 (m, 3H), 1.74-1.69 (m, 4H), 1.57-1.48 (m, 6H).

[1809] Mass (m/e) 391 (M+1)

[1810]

[1811] EXAMPLE 156: Synthesis of 1-[2-(5-cyclopentyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)ethanone

[1812] 14.5 mg of the title compound was obtained in a yield of 81% in the same manner as in EXAMPLE 114, except that 15.8 mg (0.044 mmol) of 2-bromo-1-[(S)-2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone was synthesized in PREPARATION 113, 17.6 mg (0.132 mmol) of 2-methoxymethoxy-1,1-dimethyl-ethylamine and 12.2 mg (0.088 mmol) of potassium carbonate were used.

[1813] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.41-5.38 (m, 1H), 4.61-4.53 (m, 2H), 3.80-3.70 (m, 1H), 3.60-3.53 (m, 1H), 3.45-3.30 (m, 7H), 2.35-2.30 (m, 1H), 2.17-1.98 (m, 8H), 1.87-1.79 (m, 2H), 1.75-1.70 (m, 2H), 1.09 (s, 6H).

[1814] Mass (m/e) 409 (M+1)

[1815]

[1816] EXAMPLE 157: Synthesis of 1-[2-(5-cyclopentyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)ethanone

[1817] 9.6 mg of the title compound was obtained in a yield of 69% in the same manner as
in EXAMPLE 114, except that 13.2 mg (0.037 mmol) of  
2-bromo-1-[(S)-2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone 
synthesized in PREPARATION 113, 11.4 mg (0.111 mmol) of 
2-methoxy-1,1-dimethyl-ethylamine and 10.2 mg (0.074 mmol) of potassium 
carbonate were used.  

[1818] \( ^{1}H\) NMR (CDCl \_3) \( \delta\) 5.41-5.37 (m, 1H), 375-370 (m, 1H), 365-355 (m, 1H), 
345-338 (m, 3H), 332 (s, 3H), 324-318 (m, 2H), 235-228 (m, 1H), 2.16-1.98 (m, 
8H), 1.84-1.82 (m, 2H), 1.73-1.70 (m, 2H), 1.06 (s, 6H).

[1819] Mass (m/e) 379 (M+1)

[1820]

[1821] EXAMPLE 158: Synthesis of 1-[2-[5-(4-fluoro-phenyl)-[1,2,4] oxadiazole-
3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[1822] 39 mg of the title compound was obtained in a yield of 26% in the same manner as 
in EXAMPLE 114, except that 14.5 mg (0.038 mmol) of  
2-bromo-1-[(S)-2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl] 
-ethanone synthesized in PREPARATION 111, 10.1 mg (0.114 mmol) of 
2-hydroxy-1,1-dimethyl-methylamine and 10.5 mg (0.076 mmol) of potassium 
carbonate were used.

[1823] \( ^{1}H\) NMR (CDCl \_3) \( \delta\) 826-821 (m, 2H), 7.28-7.22 (m, 2H), 5.46-530 (m, 1H), 
375-371 (m, 1H), 361-359 (m, 1H), 346-340 (m, 2H), 242-238 (m, 1H), 2.19-2.05 
(m, 5H), 1.06 (s, 6H).

[1824] Mass (m/e) 391 (M+1)

[1825]

[1826] EXAMPLE 159: Synthesis of 1-[2-[5-(4-fluoro-phenyl)-[1,2,4] oxadiazole-
3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

[1827] 9.8 mg of the title compound was obtained in a yield of 58% in the same manner as 
in EXAMPLE 114, except that 15.0 mg (0.039 mmol) of  
2-bromo-1-[(S)-2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl] 
-ethanone synthesized in PREPARATION 111, 16.0 mg (0.118 mmol) of 
2-methoxymethoxy-1,1-dimethyl-ethylamine and 11.0 mg (0.078 mmol) of potassium 
carbonate were used.

[1828] \( ^{1}H\) NMR (CDCl \_3) \( \delta\) 825-820 (m, 2H), 7.27-7.21 (m, 2H), 5.45-5.42 (m, 1H), 4.61 
(s, 2H), 377-371 (m, 1H), 365-361 (m, 1H), 347-346 (m, 2H), 338-328 (m, 5H), 
2.40-2.36 (m, 1H), 2.17-2.03 (m, 4H), 1.10 (s, 6H).
EXAMPLE 160: Synthesis of 1-[2-[5-(4-fluoro-phenyl)-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

6.9 mg of the title compound was obtained in a yield of 45% in the same manner as in EXAMPLE 114, except that 14.6 mg (0.038 mmol) of 2-bromo-1-[(S)-2-[5-(4-fluoro-phenyl)-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 111, 11.9 mg (0.115 mmol) of 2-methoxy-1,1-dimethyl-ethylamine and 10.6 mg (0.076 mmol) of potassium carbonate were used.

1H NMR (CDCl3) δ 8.25-8.21 (m, 2H), 7.26-7.21 (m, 2H), 5.45-5.41 (m, 1H), 3.77-3.71 (m, 1H), 3.64-3.61 (m, 1H), 3.52-3.43 (m, 2H), 3.32 (s, 3H), 3.18 (s, 2H), 2.40-2.36 (m, 1H), 2.17-2.03 (m, 4H), 1.07 (s, 6H).

EXAMPLE 161: Synthesis of 2-tert-butyllamino-1-[2-[5-(4-fluoro-phenyl)-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

5.9 mg of the title compound was obtained in a yield of 50% in the same manner as in EXAMPLE 114, except that 11.1 mg (0.029 mmol) of 2-bromo-1-[(S)-2-[5-(4-fluoro-phenyl)-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 111, 6.4 mg (0.087 mmol) of tert-butyllamine and 80 mg (0.058 mmol) of potassium carbonate were used.

1H NMR (CDCl3) δ 8.27-8.21 (m, 2H), 7.29-7.21 (m, 2H), 5.45-5.42 (m, 1H), 3.77-3.72 (m, 1H), 3.67-3.63 (m, 1H), 3.52-3.41 (m, 2H), 2.41-2.38 (m, 1H), 2.18-2.05 (m, 3H), 1.77 (br s, 1H), 1.12 (s, 9H).

EXAMPLE 162: Synthesis of 1-[2-(5-cyclopropyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

84 mg of the title compound was obtained in a yield of 53% in the same manner as in EXAMPLE 114, except that 136 mg (0.041 mmol) of 2-bromo-1-[(S)-2-(5-cyclopropyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 110, 16.6 mg (0.124 mmol) of
2-methoxymethoxy-1,1-dimethyl-ethylamine and 11.4 mg (0.083 mmol) of potassium carbonate were used.

1H NMR (CDCl₃) δ 5.40-5.36 (m, 1H), 4.63-4.56 (m, 2H), 3.75-3.70 (m, 1H), 3.68-3.60 (m, 1H), 3.46 (s, 2H), 3.40-3.33 (m, 3H), 2.30-2.20 (m, 2H), 2.20-2.02 (m, 4H), 1.37-1.28 (m, 4H), 1.11 (s, 6H).

Mass (m/e) 381 (M+1)

EXAMPLE 163: Synthesis of 1-[2-(5-cyclopropyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

53 mg of the title compound was obtained in a yield of 49% in the same manner as in EXAMPLE 114, except that 10.2 mg (0.031 mmol) of 2-bromo-1-((S)-2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)-ethanonesynthesized in PREPARATION 110, 9.8 mg (0.093 mmol) of 2-methoxy-1,1-dimethyl-ethylamine and 86 mg (0.062 mmol) of potassium carbonate were used.

1H NMR (CDCl₃) δ 5.37-5.34 (m, 1H), 3.70-3.60 (m, 1H), 3.58-3.50 (m, 1H), 3.46-3.42 (m, 2H), 3.32 (s, 3H), 3.24-3.18 (m, 2H), 2.30-2.20 (m, 2H), 2.11-1.99 (m, 3H), 1.91 (br s, 1H), 1.35-1.25 (m, 4H), 1.06 (s, 6H).

Mass (m/e) 351 (M+1)

EXAMPLE 164: Synthesis of 2-(2-benzyloxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

7.6 mg of the title compound was obtained in a yield of 66% in the same manner as in EXAMPLE 114, except that 9.2 mg (0.025 mmol) of 2-bromo-1-((S)-2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 112, 132 mg (0.074 mmol) of 1-benzyloxy-1-methyl-ethylamine and 67 mg (0.049 mmol) of potassium carbonate were used.

1H NMR (CDCl₃) δ 7.34-7.26 (m, 5H), 5.40-5.36 (m, 1H), 4.54-4.43 (m, 2H), 3.63-3.57 (m, 3H), 3.50-3.47 (m, 1H), 3.43-3.37 (m, 2H), 3.31-3.24 (m, 5H), 2.27-2.24 (m, 1H), 2.06-1.96 (m, 4H), 1.46 (s, 6H), 0.88 (d, 6H, J=80Hz).

Mass (m/e) 459 (M+1)

EXAMPLE 165: Synthesis of
2-(2-benzylxoy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

[1857] 7.6 mg of the title compound was obtained in a yield of 50% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.033 mmol) of 2-bromo-1-[(S)-2-(5-(2-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl)-ethanonesynthesized in PREPARATION 106, 17.8 mg (0.099 mmol) of 1-benzylxoy-1-methyl-ethylamine and 9.1 mg (0.066 mmol) of potassium carbonate were used.

[1858] ¹H NMR (CDCl₃) δ 734-7.25 (m, 5H), 534-531 (m, 1H), 4.54-4.42 (m, 2H), 3.64-3.59 (m, 1H), 3.52-3.36 (m, 4H), 3.31-3.23 (m, 3H), 2.66-2.60 (m, 1H), 2.25-2.21 (m, 1H), 2.08-1.96 (m, 4H), 1.09 (d, 6H, J=4.0Hz).

[1859] Mass (m/e) 387 (M+1)

[1860]

[1861] EXAMPLE 166: Synthesis of 2-(2-benzylxoy-1,1-dimethyl-ethylamino)-1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

[1862] 11.4 mg of the title compound was obtained in a yield of 42% in the same manner as in EXAMPLE 114, except that 21.0 mg (0.064 mmol) of 2-bromo-1-[(S)-2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 110, 34.4 mg (0.192 mmol) of 1-benzylxoy-1-methyl-ethylamine and 177 mg (0.128 mmol) of potassium carbonate were used.

[1863] ¹H NMR (CDCl₃) δ 736-7.24 (m, 5H), 534-530 (m, 1H), 4.54-4.42 (m, 2H), 3.65-3.55 (m, 1H), 3.49-3.35 (m, 4H), 3.26-3.23 (m, 3H), 2.27-2.24 (m, 3H), 2.10-1.96 (m, 4H), 1.34-1.26 (m, 1H), 1.09 (d, 6H, J=5.6Hz).

[1864] Mass (m/e) 413 (M+1)

[1865]

[1866] EXAMPLE 167: Synthesis of 1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone

[1867] 9.5 mg of the title compound was obtained in a yield of 59% in the same manner as in EXAMPLE 114, except that 14.0 mg (0.041 mmol) of 2-bromo-1-[(S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 108, 163 mg (0.122 mmol) of 2-methoxymethoxy-1,1-dimethyl-ethylamine and 11.2 mg (0.081 mmol) of potassium
carbonate were used.

[1868] $^1$H NMR (CDCl$_3$) $\delta$ 5.42-5.39 (m, 1H), 4.61-4.54 (m, 2H), 3.73-3.69 (m, 1H), 3.60-3.58 (m, 1H), 3.45-3.31 (m, 5H), 2.35-2.30 (m, 1H), 2.14-1.20 (m, 4H), 1.50-1.47 (m, 9H), 1.09 (s, 6H).

[1869] Mass (m/e) 397 (M+1)

[1870] EXAMPLE 168: Synthesis of 1-[2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

[1871] 4.0 mg of the title compound was obtained in a yield of 39% in the same manner as in EXAMPLE 114, except that 9.7 mg (0.028 mmol) of 2-bromo-1-[(S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 108, 12.4 mg (0.085 mmol) of 2-methoxy-1,1-dimethyl-ethylamine and 7.8 mg (0.056 mmol) of potassium carbonate were used.

[1873] $^1$H NMR (CDCl$_3$) $\delta$ 5.42-5.39 (m, 1H), 3.74-3.69 (m, 1H), 3.61-3.58 (m, 1H), 3.49-3.45 (m, 2H), 3.33 (s, 3H), 3.25-3.45 (m, 2H), 2.35-2.30 (m, 1H), 2.32-2.00 (m, 3H), 1.90 (br s, 1H), 1.49-1.47 (m, 9H), 1.07 (s, 6H).

[1874] Mass (m/e) 367 (M+1)

[1875] EXAMPLE 169: Synthesis of 2-(2-benzylxoy-1,1-dimethyl-ethylamino)-1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

[1877] 10.1 mg of the title compound was obtained in a yield of 62% in the same manner as in EXAMPLE 114, except that 127 mg (0.036 mmol) of 2-bromo-1-[(S)-2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 113, 19.2 mg (0.107 mmol) of 1-benzylxoy-1-methyl-ethylamine and 9.9 mg (0.071 mmol) of potassium carbonate were used.

[1878] $^1$H NMR (CDCl$_3$) $\delta$ 7.34-7.26 (m, 5H), 5.37-5.34 (m, 1H), 4.54-4.42 (m, 2H), 3.65-3.58 (m, 1H), 3.50-3.37 (m, 3H), 3.26-3.25 (m, 2H), 2.30-1.95 (m, 9H), 1.85-1.82 (m, 3H), 1.73-1.70 (m, 2H), 1.90 (d, 2H, J=5.6Hz).

[1879] Mass (m/e) 441 (M+1)

[1880] EXAMPLE 170: Synthesis of 2-tert-butyl-1-[2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidi
ne-1-yl)-ethanone

[1882] 5.4 mg of the title compound was obtained in a yield of 58\% in the same manner as in EXAMPLE 114, except that 9.5 mg (0.025 mmol) of 2-bromo-1-\{(S)-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl\}-ethanonesynthesized in PREPARATION 117, 5.4 mg (0.074 mmol) of tert-butylamine and 6.8 mg (0.049 mmol) of potassium carbonate were used.

[1883] $^1$H NMR (CDCl$_3$) $\delta$ 5.44-5.40 (m, 1H), 378-368 (m, 1H), 363-357 (m, 1H), 349-336 (m, 2H), 239-224 (m, 3H), 2.13-1.99 (m, 5H), 1.63-1.53 (m, 4H), 138 (s, 6H), 1.11 (s, 9H).

[1884] Mass (m/e) 377 (M+1)

[1885]

[1886] EXAMPLE 171: Synthesis of 1-\{2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl\}-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[1887] 5.5 mg of the title compound was obtained in a yield of 51\% in the same manner as in EXAMPLE 114, except that 10.5 mg (0.027 mmol) of 2-bromo-1-\{(S)-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl\}-ethanonesynthesized in PREPARATION 117, 73 mg (0.082 mmol) of 2-hydroxy-1,1-dimethyl-methylamine and 7.5 mg (0.055 mmol) of potassium carbonate were used.

[1888] $^1$H NMR (CDCl$_3$) $\delta$ 5.44-5.40 (m, 1H), 373-371 (m, 1H), 358-356 (m, 1H), 348-343 (m, 2H), 320 (s, 2H), 2.40-2.24 (m, 3H), 2.13-2.05 (m, 5H), 1.64-1.54 (m, 5H), 1.39-1.38 (m, 6H), 1.07 (s, 6H).

[1889] Mass (m/e) 393 (M+1)

[1890]

[1891] EXAMPLE 172: Synthesis of 2-(1-hydroxymethyl-cyclopentylamino)-1-\{2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl\}-ethanone

[1892] 5.5 mg of the title compound was obtained in a yield of 50\% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.026 mmol) of 2-bromo-1-\{(S)-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl\}-ethanonesynthesized in PREPARATION 117, 9.0 mg (0.078 mmol) of 1-amino-1-cyclopentane ethanol and 7.2 mg (0.052 mmol) of potassium carbonate were used.

[1893] $^1$H NMR (CDCl$_3$) $\delta$ 5.44-5.40 (m, 1H), 373-368 (m, 1H), 360-352 (m, 1H), 344
(s, 2H), 324 (s, 2H), 238-224 (m, 3H), 2.13-2.03 (m, 4H), 1.90 (br s, 1H), 1.72-1.39 (m, 14H).

[1894] Mass (m/e) 419 (M+1)

[1895]

[1896] **EXAMPLE 173:** Synthesis of
2-tert-butyramino-1-{2-[5-(2-methoxy-phenyl)-1,2,4]oxadiazole-3-carbonyl]-pyrroldine-1-yl}-ethanone

[1897] 5.7 mg of the title compound was obtained in a yield of 68% in the same manner as in EXAMPLE 114, except that 85 mg (0.022 mmol) of 2-bromo-1-{(S)-2-[5-(2-methoxy-phenyl)-1,2,4]oxadiazole-3-carbonyl]-pyrroldine-1-yl}-ethanonesynthesized in PREPARATION 118, 4.7 mg (0.065 mmol) of tert-butylamine and 5.9 mg (0.043 mmol) of potassium carbonate were used.

[1898] H NMR (CDCl₃) δ 8.16-8.13 (m, 1H), 7.60-7.55 (m, 1H), 7.11-7.06 (m, 2H), 5.49-5.45 (m, 1H), 4.01-3.99 (m, 3H), 3.77-3.73 (m, 1H), 3.64-3.62 (m, 1H), 3.56-3.43 (m, 2H), 2.42-2.38 (m, 1H), 2.17-1.90 (m, 4H), 1.13 (s, 9H).

[1899] Mass (m/e) 387 (M+1)

[1900]

[1901] **EXAMPLE 174:** Synthesis of
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-{2-[5-(2-methoxy-phenyl)-1,2,4]oxadiazole-3-carbonyl]-pyrroldine-1-yl}-ethanone

[1902] 4.1 mg of the title compound was obtained in a yield of 41% in the same manner as in EXAMPLE 114, except that 97 mg (0.025 mmol) of 2-bromo-1-{(S)-2-[5-(2-methoxy-phenyl)-1,2,4]oxadiazole-3-carbonyl]-pyrroldine-1-yl}-ethanonesynthesized in PREPARATION 118, 6.6 mg (0.074 mmol) of 2-hydroxy-1,1-dimethyl-methylamine and 6.8 mg (0.049 mmol) of potassium carbonate were used.

[1903]

[1904] **EXAMPLE 175:** Synthesis of
2-(1-hydroxymethyl-cyclopentylamino)-1-{2-[5-(2-methoxy-phenyl)-1,2,4]oxadiazole-3-carbonyl]-pyrroldine-1-yl}-ethanone

[1905] 5.9 mg of the title compound was obtained in a yield of 58% in the same manner as in EXAMPLE 114, except that 93 mg (0.024 mmol) of 2-bromo-1-{(S)-2-[5-(2-methoxy-phenyl)-1,2,4]oxadiazole-3-carbonyl]-pyrroldine-1-yl}-ethanonesynthesized in PREPARATION 118, 82 mg (0.071 mmol) of 1-amino-1-cyclopentane ethanol and 6.5 mg (0.047 mmol) of potassium carbonate
were used.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 8.17-8.14 \text{ (m, 1H), 7.60-7.56 (m, 1H), 7.11-7.07 (m, 2H),} \\
5.49-5.45 \text{ (m, 1H), 4.01-3.99 (m, 3H), 3.75-3.70 (m, 1H), 3.60-3.56 (m, 1H), 3.45 (s,} \\
2\text{H), 3.24 (s, 2H), 2.42-2.39 (m, 1H), 2.17-1.80 (m, 6H), 1.73-1.68 \text{ (m, 2H), 1.60-1.47} \\
\text{ (m, 7H).} \]

Mass (m/e) 429 (M+1)

\[ \text{EXAMPLE 176: Synthesis of} \\
2-\{2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino\}-1-\{2-(5-methyl-[1,2,4]oxadiazol} \\
e-3-carbonyl\}-pyrroldine-1-yl\}-ethanone \\
\]

4.8 mg of the title compound was obtained in a yield of 40% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.033 mmol) of
2-bromo-[2S-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrroldine-1-yl]-ethanonesynthes
ized in PREPARATION 106, 14.6 mg (0.099 mmol) of
2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamine and 9.1 mg (0.066 mmol) of
potassium carbonate were used.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 5.28-5.34 \text{ (m, 1H), 3.73-3.68 (m, 1H), 3.63-3.56 (m, 3H),} \\
3.54-3.52 \text{ (m, 2H), 3.49-3.47 (m, 2H), 3.37-3.35 (m, 3H), 3.30 (s, 2H), 2.67 (s, 3H),} \\
2.37-2.28 (m, 1H), 2.17-2.00 (m, 4H), 1.08 (s, 6H). \]

Mass (m/e) 367 (M+1)

\[ \text{EXAMPLE 177: Synthesis of} \\
2-\{2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino\}-1-\{2-[5-(1-methyl-cyclohexyl)-[} \\
1,2,4]oxadiazole-3-carbonyl\}-pyrroldine-1-yl\}-ethanone \\
\]

88 mg of the title compound was obtained in a yield of 68% in the same manner as in EXAMPLE 114, except that 11.0 mg (0.029 mmol) of
2-bromo-1-{(S)-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrroldine \\
-1-yl}-ethanonesynthesized in PREPARATION 117, 12.6 mg (0.086 mmol) of
2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamine and 80 mg (0.057 mmol) of
potassium carbonate were used.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 5.44-5.41 \text{ (m, 1H), 3.72-3.69 (m, 1H), 3.61-3.57 (m, 3H),} \\
3.55-3.49 \text{ (m, 4H), 3.37-3.36 (m, 3H), 3.33-3.19 (m, 2H), 2.38-2.23 (m, 3H), 2.17-2.01} \\
\text{ (m, 4H), 1.65-1.49 (m, 5H), 1.38 (s, 6H), 1.09 (s, 6H).} \]

Mass (m/e) 451 (M+1)

\[ \text{EXAMPLE 178: Synthesis of} \\
2-\{2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino\}-1-\{2-[5-(1-methyl-cyclohexyl)]-[} \\
1,2,4]oxadiazole-3-carbonyl\}-pyrroldine-1-yl\}-ethanone \\
\]

184 mg of the title compound was obtained in a yield of 80% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.029 mmol) of
2-bromo-1-{(S)-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrroldine \\
-1-yl}-ethanonesynthesized in PREPARATION 117, 12.6 mg (0.086 mmol) of
2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamine and 80 mg (0.057 mmol) of
potassium carbonate were used.

\[ \text{H NMR (CDCl}_3 \text{)} \delta 5.42-5.41 \text{ (m, 1H), 3.72-3.69 (m, 1H), 3.61-3.57 (m, 3H),} \\
3.55-3.49 \text{ (m, 4H), 3.37-3.36 (m, 3H), 3.33-3.19 (m, 2H), 2.38-2.23 (m, 3H), 2.17-2.01} \\
\text{ (m, 4H), 1.65-1.49 (m, 5H), 1.38 (s, 6H), 1.09 (s, 6H).} \]

Mass (m/e) 451 (M+1)
EXAMPLE 178: Synthesis of 1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino]-ethanone

7.4 mg of the title compound was obtained in a yield of 64% in the same manner as in EXAMPLE 114, except that 9.8 mg (0.026 mmol) of 2-bromo-1-[(S)-2-[5-(2-methoxy-1,1-dimethyl-ethyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 112, 6 mg (0.078 mmol) of 2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamine and 7.2 mg (0.052 mmol) of potassium carbonate were used.

1H NMR (CDCl₃) δ 5.43-5.39 (m, 1H), 374-370 (m, 1H), 361-348 (m, 9H), 337-328 (m, 8H), 234-230 (m, 1H), 211-200 (m, 4H), 1.46 (s, 6H), 1.08 (s, 6H).

Mass (m/e) 441 (M+1)

EXAMPLE 179: Synthesis of 1-[2-(5-adamantane-1-yl-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-tert-butyamino-ethanone

4.8 mg of the title compound was obtained in a yield of 50% in the same manner as in EXAMPLE 114, except that 9.8 mg (0.023 mmol) of 2-bromo-1-[(S)-2-(5-adamantyl-1-yl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 115, 5.1 mg (0.069 mmol) of tert-butyamine and 6.4 mg (0.046 mmol) of potassium carbonate were used.

1H NMR (CDCl₃) δ 5.45-5.33 (m, 1H), 379-370 (m, 1H), 366-360 (m, 1H), 354-339 (m, 2H), 241-234 (m, 1H), 218-1.94 (m, 15H), 1.82-1.79 (m, 3H), 1.14 (s, 9H).

Mass (m/e) 415 (M+1)

EXAMPLE 180: Synthesis of 1-[2-(5-adamantane-1-yl-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

4.7 mg of the title compound was obtained in a yield of 47% in the same manner as in EXAMPLE 114, except that 9.8 mg (0.023 mmol) of 2-bromo-1-[(S)-2-(5-adamantyl-1-yl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 115, 6.2 mg (0.070 mmol) of 2-hydroxy-1,1-dimethyl-methyamine and 6.4 mg (0.046 mmol) of potassium carbonate were used.

1H NMR (CDCl₃) δ 5.42-5.38 (m, 1H), 375-364 (m, 1H), 360-352 (m, 1H), 344 (s, 2H), 327-320 (m, 2H), 240-232 (m, 1H), 212-2.04 (m, 13H), 1.80-1.70 (m, 8H),...
1.60-1.49 (m, 7H).

[1932] Mass (m/e) 431 (M+1)

[1933]

[1934] **EXAMPLE 181:** Synthesis of 1-[2-(5-adamantane-1-yl)-1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[1935] 4.6 mg of the title compound was obtained in a yield of 49% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.024 mmol) of 2-bromo-1-[(S)-2-(5-adamantyl-1-yl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 115, 82 mg (0.071 mmol) of 1-amino-1-cyclopentane ethanol and 6.6 mg (0.047 mmol) of potassium carbonate were used.

[1936] $^1$H NMR (CDCl$_3$) $\delta$ 5.42-5.39 (m, 1H), 3.77-3.64 (m, 1H), 3.61-3.52 (m, 1H), 3.50-3.40 (m, 1H), 3.24-3.17 (m, 2H), 2.41-2.32 (m, 2H), 2.12-2.02 (m, 13H), 1.83-1.76 (m, 6H), 1.07 (s, 6H). Mass (m/e) 457 (M+1)

[1937]

[1938] **EXAMPLE 182:** Synthesis of 2-tert-butylamino-1-[2-[5-(1-methyl-cyclopropyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[1939] 4.2 mg of the title compound was obtained in a yield of 43% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.029 mmol) of 2-bromo-1-[(S)-2-[5-(1-methyl-cyclopropyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 114, 6.4 mg (0.088 mmol) of tert-butyl and 81 mg (0.058 mmol) of potassium carbonate were used.

[1940] $^1$H NMR (CDCl$_3$) $\delta$ 5.37-5.34 (m, 1H), 3.76-3.67 (m, 1H), 3.62-3.56 (m, 1H), 3.47-3.36 (m, 2H), 2.37-2.28 (m, 1H), 2.18-1.84 (m, 5H), 1.59 (s, 3H), 1.52-1.49 (m, 2H), 1.10 (s, 9H).

[1941] Mass (m/e) 335 (M+1)

[1942]

[1943] **EXAMPLE 183:** Synthesis of 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(1-methyl-cyclopropyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[1944] 6.9 mg of the title compound was obtained in a yield of 48% in the same manner as in EXAMPLE 114, except that 14.0 mg (0.041 mmol) of 2-bromo-1-[(S)-2-[5-(1-methyl-cyclopropyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 114, 11.0 mg (0.123 mmol) of
2-hydroxy-1,1-dimethyl-methylenamine and 113 mg (0.082 mmol) of potassium carbonate were used.

\[1\] H NMR (CDCl\textsubscript{3}) \( \delta \) 5.41-5.37 (m, 1H), 379-370 (m, 1H), 3.63-3.56 (m, 1H), 3.24 (s, 2H), 3.27-3.19 (m, 2H), 3.10-2.50 (br s, 2H), 2.40-233 (m, 1H), 2.17-2.03 (m, 3H), 1.65-1.63 (m, 4H), 1.55-1.53 (m, 2H), 1.11 (s, 6H).

\[2\] Mass (m/e) 351 (M+1)

\[3\] EXAMPLE 184: Synthesis of 2-(1-hydroxymethyl-cyclopentylamino)-1-(2-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazo-3-carbonyl]-pyrrolidine-1-yl)-ethanone

5.8 mg of the title compound was obtained in a yield of 53% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.029 mmol) of 2-bromo-1-[(S)-2-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazo-3-carbonyl]-pyrrolidine-1-yl]-ethanonesynthesized in PREPARATION 114, 10.1 mg (0.088 mmol) of 1-amino-1-cyclopentane ethanol and 81 mg (0.058 mmol) of potassium carbonate were used.

\[4\] H NMR (CDCl\textsubscript{3}) \( \delta \) 538-535 (m, 1H), 372-366 (m, 1H), 3.59-3.52 (m, 1H), 3.42 (s, 2H), 3.26-3.20 (m, 2H), 2.46-232 (m, 1H), 2.17-1.95 (m, 4H), 1.77-1.66 (m, 2H), 1.62-1.44 (m, 12H), 1.10-1.07 (m, 2H).

\[5\] Mass (m/e) 377 (M+1)

\[6\] EXAMPLE 185: Synthesis of N-(2-[2-[2-(5-tert-butyl-[1,3,4] oxadiazo-2-carbonyl]-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propyl)-acetaamide

6.5 mg (0.019 mmol) of 2-(2-amino-1,1-dimethyl-ethylamino)-1-[2S-(5-methyl-[1,3,4]oxadiazo-2-carbonyl)-pyrrolidine-1-yl]-ethanone was dissolved in 2 ml of N,N-dimethylformamide, and 77 \( \mu \)l (0.056 mmol) of triethylamine was added thereto at room temperature. 34 \( \mu \)l (0.056 mmol) of acetyl chloride was dissolved in 0.15 ml of N,N-dimethylformamide and then slowly added to the solution previously formed. After stirring for 30 minutes, Prep-TLC was conducted to isolate and yield 0.6 mg of of the title compound in a yield of 8%.

\[7\] H NMR (CDCl\textsubscript{3}) \( \delta \) 6.47 (br s, 1H), 5.45-5.41 (m, 1H), 3.78-3.65 (m, 1H), 3.62-3.56 (m, 1H), 3.49 (s, 6H), 3.40 (s, 2H), 3.18-2.96 (m, 2H), 2.48-2.40 (m, 1H), 2.24-1.97 (m, 6H), 1.31-1.06 (m, 9H).

\[8\] Mass (m/e) 394 (M+1)
EXAMPLE 186: Synthesis of \(N\)-(2-(acetyl-[2-(2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethyl)-amino)-2-methyl-propyl]-acetamide

0.6 mg of the title compound was obtained in a yield of 8% in the same manner as in EXAMPLE 114, except that 6.5 mg (0.019 mmol) of 2-(2-amino-1,1-dimethyl-ethylamino)-1-[2S-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone, 77 \(\mu\)l (0.056 mmol) of triethylamine and 3.4 \(\mu\)l (0.056 mmol) of acetyl chloride were used.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.51-5.48 (m, 1H), 1.14 (br s, 2H), 3.86-3.70 (m, 2H), 3.68-3.65 (m, 1H), 2.56-2.47 (m, 1H), 2.24-2.10 (m, 3H), 2.04-2.01 (m, 3H), 1.83 (s, 3H), 1.54-1.45 (m, 8H), 1.37-1.28 (m, 9H).

Mass (m/e) 436 (M+1)

EXAMPLE 187: Synthesis of 6-(2-methyl-2-[2-(2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethylamino)-propylamino)-pyridine-3-sulfonic acid dimethyl amide

7.9 mg of the title compound was obtained in a yield of 20% in the same manner as in EXAMPLE 114, except that 21.6 mg (0.079 mmol) of 2-bromo-1-[(S)-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 106 and 80 mg (0.027 mmol) of 6-(2-amino-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide synthesized by a method as disclosed in WO 02/051836 were used.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 843 (d, 1H, J=2.4Hz), 7.63 (dd, 1H, J=2.4Hz, 8Hz), 6.43 (d, 1H, J=8Hz), 6.02-5.99 (m, 1H), 5.37-5.33 (m, 1H), 3.73-3.66 (m, 1H), 3.60-3.54 (m, 1H), 3.47-3.38 (m, 2H), 3.36-3.19 (m, 2H), 2.72-2.67 (m, 6H), 2.66 (s, 3H), 2.41-2.32 (m, 1H), 2.19-2.00 (m, 3H), 1.14-1.13 (m, 6H).

Mass (m/e) 494 (M+1)

EXAMPLE 188: Synthesis of 2-tert-butylamino-1-[(4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone

3.1 mg of the title compound was obtained in a yield of 52% in the same manner as in EXAMPLE 114, except that 6.1 mg (0.019 mmol) of 2-bromo-1-[(2S,4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1
-yl]-ethanone synthesized in PREPARATION 120, 2.8 mg (0.038 mmol) of tert-butylamine and 10.6 mg (0.076 mmol) of potassium carbonate were used.

\[1970\]  
\( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 5.54-5.35 (m, 2H), 4.00-3.87 (m, 2H), 3.64-3.35 (m, 4H), 2.74-2.64 (m, 2H), 2.27-2.00 (m, 2H), 1.25-1.07 (m, 9H).

\[1971\]  
Mass (m/e) 313 (M+1)

\[1972\]  

\[1973\]  
**EXAMPLE 189: Synthesis of 1-[(4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone**

\[1974\]  
31 mg of the title compound was obtained in a yield of 45% in the same manner as in EXAMPLE 114, except that 6.7 mg (0.021 mmol) of 2-bromo-1-[(2S,4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 120, 37 mg (0.042 mmol) of 2-hydroxy-1,1-dimethyl-methylamine and 11.6 mg (0.084 mmol) of potassium carbonate were used.

\[1975\]  
\( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 5.54-5.46 (m, 2H), 3.95-3.87 (m, 2H), 3.58-3.17 (m, 4H), 2.73-2.68 (m, 4H), 2.28-2.12 (m, 3H), 1.07-1.03 (m, 6H).

\[1976\]  
Mass (m/e) 329 (M+1)

\[1977\]  

\[1978\]  
**EXAMPLE 190: Synthesis of 2-tert-butylamino-1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-ethanone**

\[1979\]  
(Method A) 4.8 mg of the title compound was obtained in a yield of 82% in the same manner as in EXAMPLE 114, except that 6.0 mg (0.017 mmol) of 2-bromo-1-[(2S,4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 121, 24 mg (0.033 mmol) of tert-butylamine and 9.2 mg (0.066 mmol) of potassium carbonate were used.

\[1980\]  
(Method B) 32 mg of the title compound was obtained in a yield of 35% in the same manner as in Method A above, except that 9.4 mg (0.026 mmol) of 2-bromo-1-[(2R,4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 124 and 57 mg (0.078 mmol) of tert-butylamine were used.

\[1981\]  
\( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 5.54-5.46 (m, 2H), 4.03-3.85 (m, 2H), 3.53-3.27 (m, 2H), 2.75-2.62 (m, 1H), 2.25-2.12 (m, 1H), 1.81 (br s, 1H), 1.50-1.45 (m, 9H), 1.13-0.93 (m, 9H).
[1982] Mass (m/e) 355 (M+1)

[1983]

[1984] EXAMPLE 191: Synthesis of 1-[(4S)-2-(5-tert-butyl-1,2,4] oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

[1985] (Method A) 3.6 mg of the title compound was obtained in a yield of 51% in the same manner as in EXAMPLE 114, except that 6.8 mg (0.019 mmol) of 2-bromo-1-[(2S,4S)-2-(5-tert-butyl-1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 121, 33 mg (0.038 mmol) of 2-hydroxy-1,1-dimethyl-methylamine and 10.5 mg (0.076 mmol) of potassium carbonate were used.

[1986] (Method B) 6.0 mg of the title compound was obtained in a yield of 45% in the same manner as in Method A above, except that 12.9 mg (0.036 mmol) of 2-bromo-1-[(2R,4S)-2-(5-tert-butyl-1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 124 and 9.5 mg (0.107 mmol) of 2-hydroxy-1,1-dimethyl-methylamine were used.

[1987] \(^1\text{H NMR (CDCl}_3\) \(\delta\) 5.57-5.31 (m, 2H), 4.04-3.89 (m, 2H), 3.59-3.15 (m, 4H), 2.78-2.67 (m, 2H), 2.35-2.03 (m, 2H), 1.54-1.47 (m, 9H), 1.11-1.10 (m, 6H).

[1988] Mass (m/e) 371 (M+1)

[1989]

[1990] EXAMPLE 192: Synthesis of 1-[(4S)-2-(5-tert-butyl-1,2,4] oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone

[1991] 4.8 mg of the title compound was obtained in a yield of 35% in the same manner as in EXAMPLE 114, except that 11.0 mg (0.030 mmol) of 2-bromo-1-[(2S,4S)-2-(5-tert-butyl-1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 121, 153 mg (0.076 mmol) of 2-amino-2-methyl-1-phenyl-propane-1-ol and 17.0 mg (0.121 mmol) of potassium carbonate were used.

[1992] \(^1\text{H NMR (CDCl}_3\) \(\delta\) 7.38-7.24 (m, 5H), 5.58-5.30 (m, 2H), 4.47-4.35 (m, 1H), 3.97-3.89 (m, 2H), 3.62-3.41 (m, 2H), 2.80-2.05 (m, 4H), 1.52-1.43 (m, 9H), 1.09-0.85 (m, 6H). Mass (m/e) 447 (M+1)

[1993]

[1994] EXAMPLE 193: Synthesis of 2-tert-butylamino-1-[(4S)-2-[5-(1,1-dimethyl-propyl)-1,2,4]oxadiazole-3-carbonyl
4-fluoro-pyrrolidine-1-yl)-ethane

[1995] 4.7 mg of the title compound was obtained in a yield of 53% in the same manner as in EXAMPLE 114, except that 9.0 mg (0.024 mmol) of 2-bromo-1-{(2S,4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl}-ethane synthesized in PREPARATION 122, 53 mg (0.072 mmol) of tert-butylamine and 7.0 mg (0.048 mmol) of potassium carbonate were used.

[1996] 1H NMR (CDCl₃) δ 5.55-5.33 (m, 2H), 4.00-3.89 (m, 2H), 3.50-3.33 (m, 2H), 2.75-2.50 (m, 2H), 2.20-2.00 (m, 1H), 1.94 (br s, 2H), 1.82 (q, 2H, J=7.6Hz), 1.48-1.44 (m, 6H), 1.08 (s, 6H), 0.84 (t, 3H, J=7.6Hz).

[1997] Mass (m/e) 369 (M+1)

[1998]

[1999] EXAMPLE 194: Synthesis of 1-{(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl}-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethane

[2000] 4.9 mg of the title compound was obtained in a yield of 53% in the same manner as in EXAMPLE 114, except that 9.0 mg (0.024 mmol) of 2-bromo-1-{(2S,4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl}-ethane synthesized in PREPARATION 122, 6.4 mg (0.072 mmol) of 2-hydroxy-1,1-dimethyl-methyamine and 7.0 mg (0.048 mmol) of potassium carbonate were used.

[2001] 1H NMR (CDCl₃) δ 5.55-5.34 (m, 2H), 3.99-3.80 (m, 2H), 3.57-3.33 (m, 2H), 3.28-3.13 (m, 2H), 2.76-2.64 (m, 2H), 2.25-2.11 (m, 1H), 1.83 (q, 2H, J=7.6Hz), 1.49-1.42 (m, 6H), 1.07-0.97 (m, 6H), 0.84 (t, 3H, J=7.6Hz).

[2002] Mass (m/e) 385 (M+1)

[2003]

[2004] EXAMPLE 195: Synthesis of 1-{(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl}-2-(1-hydroxymethyl-cyclopentylamino)-ethane

[2005] 6.6 mg of the title compound was obtained in a yield of 67% in the same manner as in EXAMPLE 114, except that 9.0 mg (0.024 mmol) of 2-bromo-1-{(2S,4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl}-ethane synthesized in PREPARATION 122, 83 mg (0.072 mmol) of 1-amino-1-cyclopentyl-propene alcohol and 7.0 mg (0.048 mmol) of potassium carbonate were used.

[2006] 1H NMR (CDCl₃) δ 5.56-5.16 (m, 2H), 4.17-3.69 (m, 2H), 3.56-3.29 (m, 2H),
3.26-3.18 (m, 2H), 2.75-2.50 (m, 2H), 2.30-2.00 (m, 2H), 1.83 (q, 2H, J=7.6Hz),
1.71-1.58 (m, 2H), 1.55-1.43 (m, 1H), 0.85 (t, 3H, J=7.6Hz).

[2007] Mass (m/e) 411 (M+1)

[2008]

[2009] **EXAMPLE 196: Synthesis of 1-[(4S)-2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-4-fluoro-pyrroline-1-y]-2-(1-hydroxymethyl-cyclopentylamo)-ethanone**

[2010] 6.1 mg of the title compound was obtained in a yield of 43% in the same manner as in EXAMPLE 114, except that 130 mg (0.036 mmol) of 2-bromo-1-[(2S,4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-floro-pyrroline-1-y]-ethanone synthesized in PREPARATION 121, 11.0 mg (0.072 mmol) of 1-amino-1-cyclopropentane ethanol and 22.0 mg (0.144 mmol) of potassium carbonate were used.

[2011] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 377 (br s, 1H), 5.56-5.16 (m, 1H), 4.13-3.81 (m, 1H), 3.64 (s, 2H), 3.52-3.17 (m, 3H), 279-2.66 (m, 1H), 234-211 (m, 1H), 1.90-1.87 (m, 2H), 1.76-1.66 (m, 6H), 1.56-1.46 (m, 9H).

[2012] Mass (m/e) 397 (M+1)

[2013]

[2014] **EXAMPLE 197: Synthesis of 2-tert-butyl-1-[(4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-1,2,4]oxadiazole-3-carbonyl]-pyrroline-1-y]-ethanone**

[2015] 5.4 mg of the title compound was obtained in a yield of 69% in the same manner as in EXAMPLE 114, except that 80 mg (0.020 mmol) of 2-bromo-1-[(2S,4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-1,2,4]oxadiazole-3-carbonyl]-pyrroline-1-y]-ethanone synthesized in PREPARATION 123, 4.4 mg (0.040 mmol) of tert-butylamine and 5.5 mg (0.040 mmol) of potassium carbonate were used.

[2016] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.56-5.46 (m, 2H), 4.04-3.85 (m, 2H), 3.54-333 (m, 2H), 276-2.53 (m, 2H), 2.28-2.09 (m, 3H), 1.89 (br s, 2H), 1.65-1.48 (m, 4H), 1.45-1.38 (m, 5H), 1.15-0.93 (m, 9H).

[2017] Mass (m/e) 395 (M+1)

[2018]

[2019] **EXAMPLE 198: Synthesis of 1-[(4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-y]-2-(2-hydroxy-1,1-dimethyl-ethylamo)-ethanone**

[2020] 53 mg of the title compound was obtained in a yield of 46% in the same manner as
in EXAMPLE 114, except that 113 mg (0.028 mmol) of
2-bromo-1-[(2S,4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 123, 7.5 mg (0.084 mmol) of 2-hydroxy-1,1-dimethyl-methyamine and 7.8 mg (0.056 mmol) of potassium carbonate were used.

[2021] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.56-5.19 (m, 2H), 4.03-3.80 (m, 2H), 3.59-3.14 (m, 4H), 2.80-2.50 (m, 2H), 2.27-1.95 (m, 5H), 1.61-1.4946 (m, 4H), 1.39 (br s, 2H), 1.10-0.99 (m, 9H).

[2022] Mass (m/e) 411 (M+1)

[2023]

[2024] EXAMPLE 199: Synthesis of
1-[(4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

[2025] 4.9 mg of the title compound was obtained in a yield of 51% in the same manner as in EXAMPLE 114, except that 89 mg (0.022 mmol) of
2-bromo-1-[(2S,4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 123, 7.6 mg (0.066 mmol) of 1- amino-1-cyclopentane ethanol and 6.1 mg (0.044 mmol) of potassium carbonate were used.

[2026] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.59-5.19 (m, 2H), 4.20-3.85 (m, 2H), 3.59-3.21 (m, 4H), 2.81-2.55 (m, 2H), 2.31-2.12 (m, 4H), 1.80-1.28 (m, 19H).

[2027] Mass (m/e) 437 (M+1)

[2028]

[2029] EXAMPLE 200: Synthesis of
1-[(4S)-4-fluoro-2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone

[2030] 3.4 mg of the title compound was obtained in a yield of 35% in the same manner as in EXAMPLE 114, except that 5.5 mg (0.017 mmol) of
2-bromo-1-[(2S,4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 120, 6.9 mg (0.034 mmol) of 2-amino-2-methyl-1-phenyl-propane-1-ol and 11.6 mg (0.084 mmol) of potassium carbonate were used.

[2031] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.38-7.23 (m, 1H), 5.55-5.30 (m, 2H), 4.47-4.29 (m, 1H), 4.13-3.88 (m, 2H), 3.66-3.40 (m, 2H), 2.74-2.61 (m, 4H), 2.25-2.00 (m, 1H), 1.70 (br s, 1H), 1.10-0.91 (m, 6H).
[2032] Mass (m/e) 405 (M+1)

[2033]

[2034] **EXAMPLE 201: Synthesis of**
2-(2-cyclohexyl-2-hydroxy-1,1-dimethyl-ethylamino)-1-[(4S)-4-fluoro-2-(5-methyl-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone

[2035] 1.0mg of the title compound was obtained in a yield of 12% in the same manner as in EXAMPLE 114, except that 6.5 mg (0.020 mmol) of 2-bromo-1-[(2S,4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 120, 84 mg (0.041 mmol) of 2-amino-1-cyclohexyl-2-methyl-propane-1-ol and 11.2 mg (0.081 mmol) of potassium carbonate were used.

[2036] 1H NMR (CDCl₃) δ 5.52-5.28 (m, 2H), 4.13-3.85 (m, 2H), 3.54-3.33 (m, 2H), 3.14-3.01 (m, 1H), 2.76-2.58 (m, 8H), 2.30-2.18 (m, 1H), 1.85-1.56 (m, 6H), 1.48-1.38 (m, 1H), 1.32-1.04 (m, 16H).

[2037] Mass (m/e) 411 (M+1)

[2038]

[2039] **EXAMPLE 202: Synthesis of 1-[(4S)-2-(5-tert-butyl-1,2,4 oxadiazole-3-carbonyl)-4-fluoro-2-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamine)-ethanone**

[2040] 6.6mg of the title compound was obtained in a yield of 65% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.028 mmol) of 2-bromo-1-[(2S,4S)-2-(5-tert-butyl-1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 121, 6.8 mg (0.055 mmol) of 1-hydroxymethyl-cyclopropylamine and 153 mg (0.110 mmol) of potassium carbonate were used.

[2041] 1H NMR (CDCl₃) δ 6.39 (s, 1H), 5.31-5.17 (m, 1H), 4.88 (d, 1H, 12Hz), 4.54-4.50 (m, 1H), 4.31-4.25 (m, 2H), 3.91-3.93 (m, 1H), 3.51-3.43 (m, 2H), 2.78 (d, 1H, 12Hz), 2.45-2.36 (m, 2H), 1.49-1.44 (m, 9H), 0.53-0.49 (m, 1H), 0.40-0.36 (m, 1H), 0.32-0.28 (m, 1H), 0.11-0.09 (m, 1H).

[2042] Mass (m/e) 369 (M+1)

[2043]

[2044] **EXAMPLE 203: Synthesis of 1-[(4S)-4-fluoro-2-(5-methyl-1,2,4 oxadiazole-3-carbonyl)-2-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamine)-ethanone**

[2045] 2.1mg of the title compound was obtained in a yield of 30% in the same manner as
in EXAMPLE 114, except that 7.0 mg (0.022 mmol) of 2-bromo-1-\((2S,4S)\)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 121, 5.4 mg (0.044 mmol) of 1-hydroxymethyl-cyclopropylamine and 13.1 mg (0.088 mmol) of potassium carbonate were used.

\[\text{[2046]}\]

\[\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}) } \delta 6.42 (s, 1H), 531-5.16 (m, 1H), 4.52-4.48 (m, 2H), 430-4.25 (m, 2H), 398-392 (m, 1H), 352-344 (m, 2H), 279-274 (m, 1H), 268 (s, 3H), 2.42-2.09 (m, 2H), 0.55-0.50 (m, 1H), 0.41-0.30 (m, 2H), 0.16-0.12 (m, 1H).

\[\text{[2047]}\]

Mass (m/e) 327 (M+1)

\[\text{[2048]}\]

\[\text{[2049]}\]

**EXAMPLE 204: Synthesis of 1-\((4S)\)-2-(5-tert-butyl-[1,2,4] oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone**

\[\text{[2050]}\]

4.2 mg of the title compound was obtained in a yield of 40% in the same manner as in EXAMPLE 114, except that 123 mg (0.034 mmol) of 2-bromo-1-\((2S,4S)\)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 121, 14.0 mg (0.102 mmol) of 2-methoxymethoxy-1,1-dimethyl-ethylamine and 9.4 mg (0.068 mmol) of potassium carbonate were used.

\[\text{[2051]}\]

\[\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}) } \delta 5.53-533 (m, 1H), 4.63-4.56 (m, 2H), 4.00-385 (m, 2H), 3.55-3.46 (m, 2H), 339-333 (m, 4H), 271-2.61 (m, 1H), 2.24-2.00 (m, 2H), 1.50-1.45 (m, 9H), 1.12-1.07 (m, 6H).

\[\text{[2052]}\]

Mass (m/e) 415 (M+1)

\[\text{[2053]}\]

\[\text{[2054]}\]

**EXAMPLE 205: Synthesis of 1-\((4S)\)-2-(5-methyl-[1,2,4] oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone**

\[\text{[2055]}\]

6.1 mg of the title compound was obtained in a yield of 50% in the same manner as in EXAMPLE 114, except that 11.4 mg (0.032 mmol) of 2-bromo-1-\((2S,4S)\)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 121, 9.7 mg (0.094 mmol) of 2-methoxy-1,1-dimethyl-ethylamine and 87 mg (0.063 mmol) of potassium carbonate were used.

\[\text{[2056]}\]

\[\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}) } \delta 5.56-5.49 (m, 2H), 4.00-391 (m, 2H), 354-319 (m, 6H), 2.85-2.50 (m, 2H), 2.23-2.01 (m, 2H), 1.53-1.48 (m, 9H), 1.13-1.07 (m, 6H).\]
[2059] **EXAMPLE 206:** Synthesis of 1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4] oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(3-trifluoromethyl-5,6-dihydro-o-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-ethanone

12.5 mg of the title compound was obtained in a yield of 96% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.027 mmol) of 2-bromo-1-{(2S,4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl}-ethanone synthesized in PREPARATION 122, 153 mg (0.072 mmol) of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine synthesized by a method as disclosed in WO 03/004498 were used.

[2061] $^1$H NMR (CDCl$_3$) $\delta$ 5.62-5.30 (m, 2H), 4.37-3.82 (m, 6H), 3.68-3.24 (m, 4H), 3.15-3.09 (m, 1H), 2.76-2.54 (m, 1H), 1.89-1.83 (m, 2H), 1.78-1.72 (m, 1H), 1.48 (s, 3H), 1.40-1.37 (m, 3H), 0.90-0.80 (m, 3H).

[2062] Mass (m/e) 488 (M+1)

[2063]

[2064] **EXAMPLE 207:** Synthesis of 1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4] oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(3-trifluoromethyl-5,6-dihydro-o-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-ethanone

43 mg of the title compound was obtained in a yield of 56% in the same manner as in EXAMPLE 114, except that 5.8 mg (0.015 mmol) of 2-bromo-1-{(2S,4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl}-ethanone synthesized in PREPARATION 122 and 9.5 mg (0.047 mmol) of 1-benzyl-4-methyl-piperidine-4-ylamine synthesized by a method as disclosed in EP 0647639 A1 were used.

[2066] $^1$H NMR (CDCl$_3$) $\delta$ 7.32-7.24 (m, 5H), 5.54-5.17 (m, 2H), 4.03-3.82 (m, 2H), 3.53-3.29 (m, 2H), 2.76-2.61 (m, 1H), 2.56-2.33 (m, 2H), 2.24-2.07 (m, 1H), 1.85-1.79 (m, 2H), 1.73 (brs, 2H), 1.60-1.57 (m, 4H), 1.48-1.41 (m, 7H), 1.09-1.04 (m, 3H), 0.88-0.82 (m, 3H).

[2067] Mass (m/e) 500 (M+1)

[2068]

[2069] **EXAMPLE 208:** Synthesis of

6-[2-(2-{(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propylamino]-pyridine-3-sulfonic acid dimethylamide
5.6 mg of the title compound was obtained in a yield of 53% in the same manner as in EXAMPLE 114, except that 7.0 mg (0.019 mmol) of 2-bromo-1-{(2S,4S)-2-[5-(1,1-dimethyl-propyl)-1,2,4]oxadiazole-3-carbonyl}-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 122 and 15.0 mg (0.056 mmol) of 6-(2-amino-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethyl amide synthesized by a method as disclosed in WO 02/051836 were used.

1H NMR (CDCl₃) δ 8.47 (s, 1H), 7.66 (d, 1H, J=8.8Hz), 6.49-6.44 (m, 1H), 6.01-5.90 (m, 1H), 5.57-5.24 (m, 2H), 4.05-3.84 (m, 2H), 3.59-3.21 (m, 4H), 2.72 (s, 6H), 2.80-2.40 (m, 1H), 2.28-2.03 (m, 1H), 1.84 (q, 2H, J=7.6Hz), 1.50-1.45 (m, 6H), 1.36-1.29 (m, 3H), 1.20-1.06 (m, 6H), 0.87 (m, 3H).

Mass (m/e) 568 (M+1)

EXAMPLE 209: Synthesis of 1-{(4S)-2-[5-(1,1-dimethyl-propyl)-1,2,4]oxadiazole-3-carbonyl}-4-fluoro-pyrrolidine-1-yl]-2-(4-methyl-1-pyrimidine-2-yl-piperidine-4-ylamino)-ethanone

9.0 mg of the title compound was obtained in a yield of 69% in the same manner as in EXAMPLE 114, except that 10.0 mg (0.027 mmol) of 2-bromo-1-{(2S,4S)-2-[5-(1,1-dimethyl-propyl)-1,2,4]oxadiazole-3-carbonyl}-4-fluoro-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 122, 182 mg (0.056 mmol) of 4-methyl-1-pyrimidine-2-yl-piperidine-4-ylamine synthesized by a method as disclosed in WO 02/051836 and 11.0 mg (0.080 mmol) of potassium carbonate were used.

1H NMR (CDCl₃) δ 8.29-2.26 (m, 2H), 6.45-6.42 (m, 1H), 5.55-5.28 (m, 2H), 4.04-3.76 (m, 5H), 3.51-3.25 (m, 2H), 2.76-2.58 (m, 1H), 2.25-2.11 (m, 1H), 1.85-1.81 (m, 8H), 1.68-1.41 (m, 12H), 1.31-1.25 (m, 1H), 1.19-1.12 (m, 3H), 0.87-0.82 (m, 3H).

Mass (m/e) 488 (M+1)

EXAMPLE 210: Synthesis of 1-{2-[5-(1,1-dimethyl-propyl)-1,2,4]oxadiazole-3-carbonyl}-pyrrolidine-1-yl]-2-[1,1-dimethyl-2-(pyridine-2-ylamino)-ethy lamino]-ethanone

9.4 mg of the title compound was obtained in a yield of 76.1% in the same manner as in EXAMPLE 114, except that 10.0 mg mg of 2-bromo-1-{(S)-2-[5-(1,1-dimethyl-propyl)-1,2,4]oxadiazole-3-carbonyl}-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 116 and 14 mg of 1,1-dimethyl-2-(pyridine-2-ylamino)-ethy lamine were reacted.
1H NMR (CDCl₃) δ 8.04 (1H, d, J = 5 Hz), 7.35 (1H, t, J = 8.5 Hz), 6.5 (1H, t, J = 5 Hz), 6.40 (1H, d, J = 8.5 Hz), 5.3-5.4 (1H, m), 5.1 (1H, br t), 3.7-3.8 (1H, m), 3.6-3.7 (1H, m), 3.40 (2H, Abq, J = 12 Hz), 3.21 (2H, qd, J = 14, 5 Hz), 2.3-2.4 (1H, m), 2.0-2.2 (3H, m), 1.8 (2H, q, J = 7.5 Hz), 1.42 (6H, s), 1.12 (6H, s), 0.83 (3H, t, J = 7.5 Hz)

Mass (m/e) 443 (M+1)

[EXAMPLE 211: Synthesis of 1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4] oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-[1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamino]-ethanone]

6 mg of the title compound was obtained in a yield of 49.0% in the same manner as in EXAMPLE 114, except that 10 mg of 2-bromo-1-[(2S,4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone synthesized in PREPARATION 122 and 13 mg of 1,1-dimethyl-2-(pyridine-2-ylamino)-ethyamine were reacted.

1H NMR (CDCl₃) δ 8.04 (1H, m), 7.35 (1H, m), 6.51 (1H, m), 6.40 (1H, m), 5.1-5.6 (3H, m), 3.8-4.0 (2H, m), 3.1-3.6 (4H, m), 2.6-2.8 (1H, m), 2.0-2.2 (1H, m), 1.81 (2H, q, J = 7.5 Hz), 1.43 (6H, s), 1.0-1.2 (6H, m), 0.83 (3H, t, J = 7.5 Hz)

Mass (m/e) 461 (M+1)

[EXPERIMENT 1]

Dipeptidyl Peptidase-IV (DP-IV), known as serine protease, was obtained by a modification of the known method (Tanaka T. et al, Proc. Natl. Acad. Sci. USA, (1994) 91, 3082-3086), which comprises cloning, purification by use of Baculo-Virus and activation steps. DP-IV was used to test the pharmaceutical efficacy of candidate inhibitors as follows. The cloned DP-IV was expressed in Baculo-Virus, which was purified by nickel column and then subjected to dialysis. The inhibitors synthesized in Examples were tested to determine the binding activity thereof using a fluorescent substrate, Ac-Gly-Pro-AFC. Enzyme reactions were conducted for various concentrations of inhibitors, using 100 M Ac-Gly-Pro-AFC at 25°C in a buffer solution containing 50 mM HEPES (pH 7.4), with the concentration of DP-IV being 7.1 nM. The inhibitor's IC₅₀ value was determined by measuring the amount of fluorescence emitted in a fluorescent spectrometer after allowing enzyme reaction for 1 hour, and then calculating the concentration of inhibitors exhibiting 50% inhibition of the total enzyme reaction. As the fluorescent spectrometer, Spectra MAX GeminiXS
fluorescent spectrometer from Molecular Device Co. was used and the excitation frequency and emission frequency were set to 400 nm and 505 nm, respectively.

TABLE 1 below summarizes IC\textsubscript{50} values showing the enzyme activity-inhibiting ability measured for the compounds according to EXAMPLES 1 to 211.

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**Industrial Applicability**

[2100] As can be seen from Table 1, it is clear that pyrrolidine-based compounds of Formula 1 according to the present invention are very effective in inhibiting DPP-IV activity. Accordingly, such pyrrolidine-based compounds can be used as formulations to treat or prevent DPP-IV related diseases, for example, diabetes mellitus, obesity and the like.

[2101]

[2102] Other embodiments and uses of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the scope of particular embodiments of the invention indicated by the following claims.
Claims

A pyrrolidine-based compound of Formula 1:

(1)

wherein

A is a substituent selected from the group consisting of:

(i)

(ii)

(iii)

wherein,

R4 is each independently hydrogen; optionally substituted linear, branched, or cyclic saturated or unsaturated alkyl; optionally substituted aromatic or heteroaromatic ring; or optionally substituted heterocycle; and

X is oxygen or sulfur;

B is

\[
\begin{array}{c}
R5 \\
R6 \quad \text{N} \\
\end{array}
\]

, wherein

R5 and R6 are each independently hydrogen; optionally substituted linear,
branched, or cyclic saturated or unsaturated alkyl; optionally substituted aromatic or heteroaromatic ring; optionally substituted heterocycle; or R5 and R6 together are linked to form optionally substituted cycle or heterocycle; n is 0, 1 or 2;
R3 is hydrogen, or C₁⁻C₄ alkyl;
Y is carbon, oxygen or sulfur;
provided that where Y is carbon, R1 and R2 are each independently hydrogen or halogen, and where Y is oxygen or sulfur, R1 and R2 are not present,
or a pharmaceutically acceptable non-toxic salt, physiologically hydrolyzable ester, hydrate, solvate, isomer, or prodrug thereof.

The compound according to claim 1, wherein A in Formula 1 above is a substituent of the below formula:

wherein X is O, and R4 is hydrogen or C₁⁻C₄ alkyl group.

The compound according to claim 1, wherein B in Formula 1 above is selected from the group comprising of the below substituents:

(i)

wherein R7 and R8 are each independently hydrogen, hydroxyl or amine group,

(ii)

wherein
R9 is hydrogen or C₁⁻C₄ alkyl group;
R10 and R11 are each independently hydrogen or optionally substituted lower alkyl, or R10 and R11 together are linked to form optionally substituted cycle or heterocycle group;
R12 is optionally substituted lower alkyl, optionally substituted cycloalkyl;
optionally substituted aromatic or heteroaromatic ring; or optionally substituted heterocycle; and
n is 0 or 1,

(iii)

wherein R13 and R14 are each independently hydrogen, C_1^4 alkyl, hydroxyl, optionally substituted amine, or carboxyl group, the substitution taking place at two positions among C2 to C6 positions,

(iv)

wherein R15 and R16 are each independently hydrogen, C_1^4 alkyl, hydroxyl, optionally substituted amine, or carboxyl group, and n is 0 or 1, and

(v)

wherein R17 is hydrogen or C_1^4 alkyl group, and n is 0 or 1.

[4]
The compound according to claim 3, wherein B in Formula 1 is a substituent of the below formula:

[5] The compound according to claim 4, wherein
R9, R10 and R11 are each independently hydrogen or methyl; R12 is amine, hydroxy, alkoxy, or C\textsubscript{1-4} alkyl group substituted with amine, hydroxy, alkoxy, or phenyl which is further substituted with hydroxy or halogen; and n is 0 or 1.

[6] The compound according to claim 1, wherein Y in Formula 1 above is carbone, and R1 and R2 are each independently hydrogen or fluorine atom.

[7] The compound according to claim 1, wherein the pyrrolidine-based compounds of Formula 1 is an optical isomer as represented in Formula 1a below:

\[
\begin{align*}
&\text{R2} \quad \text{R1} \\
&\text{B} \quad \text{N} \quad \text{R3} \\
&\text{O} \quad \text{O} \\
&\text{A}
\end{align*}
\]

(1a)

wherein A, B, R1, R2, R3 and Y are the same as in Formula 1.

[8] The compound according to claim 1, wherein the pyrrolidine-based compounds are the below compounds:

2-(adamantane-1-ylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(adamantane-1-ylamino)-1-[2-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(adamantane-1-ylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(cyclopentyl-methyl-amino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(cyclohexyl-methyl-amino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(3-hydroxy-adamantane-1-ylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-tert-butylamino-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-piperidinyl-ethyl-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(octahydro-
quinoline-1-yl)-ethanone
2-(2-amino-1,1-dimethyl-ethylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2,6-dimethylpiperidine-1-yl)-ethanone
2-tert-butyramino-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-amino-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-[2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino]-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxy methyl-cyclopropylamino)-ethanone
N-2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propyl)methanesulfonamide
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone
2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propionic acid tert-butyl ester
2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propionic acid
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxy methyl-cyclopentylamino)-ethanone
2-tert-butyramino-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-1-[2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone
2-tert-butylamino-1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone
2-(2-benzyl-1,1-dimethyl-ethylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-benzyl-1,1-dimethyl-ethylamino)-1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-tert-butylamino-1-[2-(5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone
2-(1-hydroxymethyl-cyclopentylamino)-1-[2-(5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone
2-tert-butylamino-1-[2-(5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-ethanone
1-[2-(5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2
- (1-hydroxymethyl-cyclopentylamino)-ethanone
2-tert-butylamino-1-\{2-[5-(1-methyl-cyclopropyl)-1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl\}-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-\{2-[5-(1-methyl-cyclopropyl)-1,3,4]oxadiazole-2-carbonyl\}-pyrrolidine-1-yl\}-ethanone
2-(1-hydroxymethyl-cyclopentylamino)-1-\{2-[5-(1-methyl-cyclopropyl)-1,3,4]oxadiazole-2-carbonyl\}-pyrrolidine-1-yl\}-ethanone
2-tert-butylamino-1-\{2-[5-(2,4,6-trimethyl-phenyl)-1,3,4]oxadiazole-2-carbonyl\}-pyrrolidine-1-yl\}-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-\{2-[5-(2,4,6-trimethyl-phenyl)-1,3,4]oxadiazole-2-carbonyl\}-pyrrolidine-1-yl\}-ethanone
2-(1-hydroxymethyl-cyclopentylamino)-1-\{2-[5-(2,4,6-trimethyl-phenyl)-1,3,4]oxadiazole-2-carbonyl\}-pyrrolidine-1-yl\}-ethanone
1-[2-[5-tert-butyl-1,3,4]oxadiazole-2-carbonyl\]-pyrrolidine-1-yl\}-2-\{(2-hydroxy-ethyl)\}-methyl-amino\}-ethanone
3-tert-butylamino-1-\{2-[5-tert-butyl-1,3,4]oxadiazole-2-carbonyl\}-pyrrolidine-1-yl\}-propane-1-one
1-[2-[5-tert-butyl-1,3,4]oxadiazole-2-carbonyl\]-pyrrolidine-1-yl\}-3-\{(2-hydroxy-ethyl)\}-methyl-amino\}-propane-1-one
1-[2-(5-tert-butyl-1,3,4]oxadiazole-2-carbonyl\]-pyrrolidine-1-yl\}-3-\{(2-hydroxy-methyl-piperidine-1-yl\)-propane-1-one
6-(2-[2-[5-tert-butyl-1,3,4]oxadiazole-2-carbonyl\]-pyrrolidine-1-yl\}-2-oxo-ethylamino\}-2-methyl-propylamino\})-pyridine-3-sulfonic acid dimethylamide
6-(2-\{3-[2-[5-tert-butyl-1,3,4]oxadiazole-2-carbonyl\]-pyrrolidine-1-yl\}-3-oxo-propylamino\})-2-methyl-propylamino\})-pyridine-3-sulfonic acid dimethylamide
1-[2-(5-tert-butyl-1,3,4]oxadiazole-2-carbonyl\]-pyrrolidine-1-yl\}-3-[3-trifluoro-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl\}-propane-1-one
1-[1-[5-(1,1-dimethyl-propyl)-1,3,4]oxadiazole-2-carbonyl\]-pyrrolidine-1-yl\}-2-[1,1-dimethyl-2-(pyridine-2-ylamino\})-ethylamino\}-ethanone
2-tert-butylamino-1-\{2S\}-\{5-tert-butyl-1,3,4]oxadiazole-2-carbonyl\}-2-methyl-pyrrolidine-1-yl\}-ethanone
1-[\{2S\}-\{5-tert-butyl-1,3,4]oxadiazole-2-carbonyl\}-2-methyl-pyrrolidine-1-yl\}-2-(2-hydroxy-1,1-dimethyl-ethylamino\})-ethanone
2-(adamantane-1-ylamino)-1-[4S-fluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl\}-2-methyl-pyrrolidine-1-yl\}-ethanone
1-[4S-fluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-2-pyrrolidine-1-yl]-2-(1-methyl-1-phenyl-ethylamino)-ethanone
2-tert-butylamino-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone
2-tert-butylamino-1-[4S-fluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[4S-fluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamino)-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone
2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino]-2-methyl-propionic acid tert-butyl ester
2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino]-2-methyl-propionic acid
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamino)-ethanone
1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone
2-tert-butylamino-1-[4S-fluoro-2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[4S-fluoro-2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[4S-fluoro-2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone
1-[4S-fluoro-2-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone
ethoxymethoxy-1,1-dimethyl-ethylamino)-ethanone
2-tert-butylamino-1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone
1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-cyclohexyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone
2-tert-butylamino-1-{4S-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl}-ethanone
1-{4S-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl}-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
2-tert-butylamino-1-{2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl}-ethanone
1-{2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl}-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-{2-[5-(1,1-dimethyl-propyl)-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl}-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
2-tert-butyl-1-{4S-fluoro-2-[5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl}-ethanone
1-{4S-fluoro-2-[5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl}-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-{4S-fluoro-2-[5-(1-methyl-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl}-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
2-tert-butyl-1-{4S-fluoro-2-[5-(2,4,6-trimethyl-phenyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl}-ethanone
1-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-((2-hydroxy-ethyl)-methyl-amino)-ethanone
1-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-3-(2-hydroxy-1,1-dimethyl-ethylamino)-propane-1-one
1-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-3-(2-hydroxy-ethyl)-methyl-amino]-propane-1-one
1-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-3-(2-hydroxymethyl-piperidine-1-yl)-propane-1-one
6-(2-[2-[5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamideme

6-(2-[3-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-4S-fluoro-pyrrolidine-1-yl]-3-oxo-ethylamino)-2-methyl-propylamino)-pyridine-3-sulfonic acid dimethylamide

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-[1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamino]-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(1-benzyl-4-methyl-piperidine-4-ylamino)-ethanone

1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-(4-methyl-1-piperidine-4-yl-piperidine-4-ylamino)-ethanone

1-(4-{2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino}-4-methyl-piperidine-1-yl)-2-hydroxy-ethanone

2-(adamantane-1-ylamino)-1-[4,4-difluoro-2-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(adamantane-1-ylamino)-1-[4R-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanone

2-(3-hydroxy-adamantane-1-ylamino)-1-[4R-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-ethanone

1-[4R-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone

1-[4-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-2-[2-methoxy-1,1-dimethyl-ethylamino]-ethanone

1-[4-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-thiazolidine-3-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone

2-tert-butylamino-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone

2-tert-butylamino-1-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-4S-fluoro-pyrrolidine-1-yl]-ethanone

2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[4S-fluoro-2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone
azo-2-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(adamantane-1-ylamino)-1-[2-(3-methyl-[1,2,4]oxadiazole-5-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(3-hydroxy-adamantane-1-ylamino)-1-[2-(3-methyl-[1,2,4]oxadiazole-5-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(adamantane-1-ylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-tert-butylamino-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(1-benzyl-2-hydroxy-1-methyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-([1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-ethanone
2-tert-butyl-1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-tert-butyl-1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-ethyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxy-methyl-cyclopropylamine)-ethanone
2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone
2-methyl-2-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(oxo-ethylamino)-propionic acid tert-butyl ester
2-tert-butylamino-1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
2-methyl-2-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(oxo-ethylamino)-propionic acid trifluoroacetate
1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(2-cyclohexyl-1,1-dimethyl-ethylamino)-ethanone
2-(1-hydroxymethyl-cyclopentylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(1-hydroxy-methyl-cyclopentylamino)-ethanone
1-[2-(5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
2-tert-butylamino-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
1-[2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
2-tert-butyl-1-[2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
1-[2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)]
-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethaneone
2-tert-butylamino-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethaneone
2-(1-hydroxymethyl-cyclopentylamino)-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethaneone
1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethaneone
2-(2-methoxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethaneone
1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethaneone
2-tert-butylamino-1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethaneone
1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethaneone
1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethaneone
1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethaneone
1-[2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethaneone
1-[2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethaneone
1-[2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethaneone
2-tert-butylamino-1-[2-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethaneone
1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethaneone
1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethaneone
2-(2-benzyloxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethaneone
2-(2-benzyloxy-1,1-dimethyl-ethylamino)-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethaneone
2-(2-benzyloxy-1,1-dimethyl-ethylamino)-1-[2-(5-cyclopropyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-methoxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone
2-(2-benzyloxy-1,1-dimethyl-ethylamino)-1-[2-(5-cyclopentyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-tert-butyl-1-[2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
1-[2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
2-(1-hydroxymethyl-cyclopentylamino)-1-[2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
2-tert-butylamino-1-[2-[5-(2-methoxy-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(2-methoxy-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
2-(1-hydroxymethyl-cyclopentylamino)-1-[2-[5-(2-methoxy-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
2-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino]-1-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-pyrrolidine-1-yl]-ethanone
2-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino]-1-[2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
1-[2-[5-(2-methoxy-1,1-dimethyl-ethyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethylamino]-ethanone
1-[2-[5-(adamantane-1-yl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-tert-butylamino-ethanone
1-[2-(5-adamantane-1-yl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[2-(5-adamantane-1-yl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
2-tert-butylamino-1-[2-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[2-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]
xadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
2-[1-hydroxymethyl-cyclopentylamino]-1-{2-[5-(1-methyl-cyclopropyl)-[1,2,4]o
xadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
N-(2-[2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]-2-oxo-e
thylamino]-2-methyl-propyl]-acetamide
N-[2-(acetyl]-[2-[2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl]-pyrrolidine-1-yl]
-2-oxo-ethyl]-amino]-2-methyl-propyl]-acetamide
6-(2-methyl-2-[2-[2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2
-oxo-ethylamino]-propylamino)-pyridine-3-sulfonic acid dimethyl amide
2-tert-butylamino-1-[(4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-p
yrrolidine-1-yl]-ethanone
1-[(4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(
2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
2-tert-butylamino-1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro
-pyrrolidine-1-yl]-ethanone
1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-
2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-
2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone
2-tert-butylamino-1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbo
nyl]-4-fluoro-pyrrolidine-1-yl]-ethanone
1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrro
lidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrro
lidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-
2-(1-hydroxymethyl-cyclopentylamino)-ethanone
2-tert-butyl-1-[(4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-car
bonyl]-pyrrolidine-1-yl]-ethanone
1-[(4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrr
olidine-1-yl]-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone
1-[(4S)-4-fluoro-2-[5-(1-methyl-cyclohexyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrr
olidine-1-yl]-2-(1-hydroxymethyl-cyclopentylamino)-ethanone
1-[(4S)-4-fluoro-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-
2-(2-hydroxy-1,1-dimethyl-2-phenyl-ethylamino)-ethanone
2-(2-cyclohexyl-2-hydroxy-1,1-dimethyl-ethylamino)-1-[(4S)-4-fluoro-2-(5-methyl-1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-ethanone
1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamine)-ethanone
1-[(4S)-4-fluoro-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-2-pyrrolidine-1-yl]-2-(1-hydroxymethyl-cyclopropylamine)-ethanone
1-[(4S)-2-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(2-methoxymethoxy-1,1-dimethyl-ethylamino)-ethanone
1-[(4S)-2-(5-methyl-[1,2,4]oxadiazole-3-carbonyl)-4-fluoro-pyrrolidine-1-yl]-2-(2-methoxy-1,1-dimethyl-ethylamino)-ethanone
1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-ethanone
1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(3-trifluoroethyl-5,6-dihydro-8H-[1,2,4]triazol[4,3-a]pyrazine-7-yl)-ethanone
6-[2-(2-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-oxo-ethylamino)-2-methyl-propylamin]-pyridine-3-sulfonic acid dimethylamide
1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(4-methyl-1-pyrimidine-2-yl-piperidine-4-ylamino)-ethanone
1-[(2-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-pyrrolidine-1-yl]-2-(1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamino)-ethanone
1-[(4S)-2-[5-(1,1-dimethyl-propyl)-[1,2,4]oxadiazole-3-carbonyl]-4-fluoro-pyrrolidine-1-yl]-2-(1,1-dimethyl-2-(pyridine-2-ylamino)-ethylamino)-ethanone.

[9] The compound according to claim 8, wherein the pyrrolidine-based compound is 2-(2-hydroxy-1,1-dimethyl-ethylamino)-1-[(4S)-fluoro-2-(5-tert-butyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidine-1-yl]-ethanone.

[10] A process for preparation of the compound of Formula 1 reacting a compound of Formula 2 below:
wherein A, R1, R2, R3 and Y are the same as defined in Formula 1; and W is a reactive group such as halogen element, with an amine compound (BH) which corresponds to substituent B in the compound of Formula 1.

The process according to claim 10 wherein the compound of Formula 2 is prepared by a process comprising Reaction Scheme below:

wherein

A, R1, R2, R3, W and Y are the same as defined in Formula 2;

PG₁ is Boc, Cbz or Fmoc wherein Boc means t-butoxycarbonyl, Cbz means benzzyloxy carbonyl, and Foc means 9-fluorenylmethoxycarbonyl;

"a" is TFA or HCl where PG₁ is Boc; H₂/Pd/C or TMSI where PG₁ is Cbz; and Et NH where PG₁ is Fmoc; and

"b" is WCH₂ COW, wherein W is the same as defined above.

The process according to claim 11 wherein the compound of Formula 3 where A is substituent (i) in the compound of Formula 1 (compound of Formula 3 is prepared by a process comprising one of Reaction Schemes below:

<Reaction 1>

<Reaction 2>
wherein

PG₁, R₁, R₂, R₃, R₄, X and Y are the same as defined in Reaction Scheme 1;

"a" is HNMe(OMe)/EDC/HOBt, wherein Me means methyl group, EDC means 1-[(dimethylamino)propyl]-3-ethylcarbo-di-imide hydrochloride and HOBt means 1-hydroxybenzotriazol hydroxide;

"b" is 1,3,4-oxadiazole/nBuLi, wherein Bu means butyl group;

"c" is CICO₂Et/ Et₃N; NaN₃; [O];

"d" is oxadiazole/nBuLi, wherein Bu means butyl group; and

"e" is Dess-Martin[O].

The process according to claim 11 wherein the compound of Formula 3 is prepared by a process comprising Reaction Scheme below:


wherein

PG₁, R₁, R₂, R₃, R₄ and Y are the same as defined in reaction scheme 1;

X is oxygen atom; and

"e" is 1,3,4-oxadiazole/nBuLi wherein Bu means butyl group.

The process according to claim 11 wherein the compound of Formula 3 where A is substituent (ii) in the compound of Formula 1 (compound of Formula 3" is
prepared by a process comprising Reaction Schemes below:

wherein
PG<sub>1</sub>, R1, R2, R3, R4 and Y are the same as in Formula 1 and Reaction Scheme 1;
PG<sub>2</sub> is alkoxyalkyl or tert-butylidemethylsilane;
"a" is NaHSO<sub>3</sub>/NaCN;
"b" is ethylvinylether/ppTs, DHP/ppTs or TBSCl/imidazole, wherein ppTs means p-toluenesulfonic acid pyridinate, DHP means dihydropyran and TBSCl is t-butyldimethylsilyl;
"c" is H<sub>2</sub>NOH;
"d" is CDI/R<sub>3</sub>CO H wherein CDI is 1,1-carbodiimide and R3 is the same as in the above;
"e" is ppTs; and
"f" is Dess-Martin periodinane.

[15] The process according to claim 14 wherein the compound of Formula 14 is prepared directly from the compound of Formula 12 by a process comprising
Reaction Scheme below:

wherein

"e" is R4CO Cl/pyridine, and the reaction is conducted at a temperature of 100 to 130°C

[16] The process according to claim 11 wherein the compound of Formula 3 where A is substituent (iii) in the compound of Formula 1 (compound of Formula 3") is prepared by a process comprising Reaction Scheme below:

wherein

PG₁, R₁, R₂, R₃, R₄ and Y are the same as in Formula 1 and Reaction Scheme 1;
"a" is NaHSO₃/NaCN;
"b" is dioxane/6N HCl;
"c" is Boc O₂, NaOH;
"d" is CDI/R3C(=NOH)NH₂, wherein CDI is 1,1-carbodiimide; and
"e" is Dess-Martin periodinane.

[17] A pharmaceutical composition for inhibiting DPP-IV activity comprising (a) a
therapeutically effective amount of a pyrrolidine-based compound of Formula 1,
and (b) a physiologically acceptable carrier, diluent, or excipient, or a
combination thereof.

[18] The pharmaceutical composition according to claim 17 wherein the phar-
maceutical composition is used to treat or prevent diseases caused by DPP-IV.

[19] The pharmaceutical composition according to claim 18 wherein the diseases
caused by DPP-IV is diabetes mellitus or obesity.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC7 C07D 413/06**

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)

IPC7 C07D 413/06

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

Korean Patents and applications for inventions since 1975.

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

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C.

See parent family annex.

Date of the actual completion of the international search

04 FEBRUARY 2005 (04.02.2005)

Date of mailing of the international search report

05 FEBRUARY 2005 (05.02.2005)

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