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(54) Title: HETEROCYCLIC COMPOUND

(57) Abstract: The present invention provides a compound having a CaMKII inhibitory action, which is expected to be useful as an agent for the prophylaxis or treatment of cardiac diseases (particularly catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure, fatal arrhythmia) and the like. The present invention relates to compounds described in Examples, or a salt thereof.

DESCRIPTION

Title of the Invention: HETEROCYCLIC COMPOUND

Technical Field

[0001]

The present invention relates to a heterocyclic compound having a calcium/calmodulin-dependent protein kinase II (sometimes to be abbreviated as "CaMKII" in the present specification) inhibitory action, which is expected to be useful as an agent for the prophylaxis or treatment of cardiac diseases (particularly catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure, fatal arrhythmia) and the like.

[0002]

(Background of the Invention)

Cardiac diseases include heart failure, arrhythmia, myocardial infarction, angina, valvular heart disease and the like, and they are high-mortality diseases. In treatment of cardiac diseases with a drug, the symptoms are improved by control of each risk factor and symptomatic therapy. However, the satisfaction with treatment remains low level, and there is now no definitive therapy.

Calcium-calmodulin complex binds to Ca^{2+}/calmodulin-dependent protein kinase (CaMK) included in serine/threonine protein kinase, and activates the kinase. The CaMK family includes CaMKII, and four isoforms (α, β, γ and δ) exist as CaMKII. CaMKII α and CaMKII β are expressed mainly in cerebral tissue, and CaMKII γ and CaMKII δ are expressed in many tissues including heart. CaMKII is activated by amino acid-modification due to oxidative stress or hyperglycemia, in addition to the binding of calcium-calmodulin complex. CaMKII regulates cell functions by phosphorylation of a transcription factor which is a substrate, a protein that plays a function in organelle uptake/excretion of Ca^{2+}, a protein that regulates contract and relax of muscles, a channel that regulates an

intracellular ion concentration, and the like, due to its kinase activation.

Some documents suggest that CaMKII plays a harmful role in progress of cardiac disease conditions. Expression and activity of CaMKII are increased in heart of human patient or animal with heart failure (Non-Patent Documents 1-4). In transgenic mouse overexpressing CaMKII δ in heart, onsets of cardiac hypertrophy and heart failure are reported (Non-Patent Document 4). By studies using an inhibitor by a pharmacological method, and studies using a gene deletion by genetic method, protecting effects on heart failure, cardiac hypertrophy, myocardial infarction and arrhythmia by an inhibition of CaMKII and an overexpression of CaMKII inhibitory protein are reported in mouse (Non-Patent Documents 5-7). For catecholaminergic polymorphic ventricular tachycardia, improving effects on disease conditions by CaMKII inhibitor in mutant ryanodine knock-in mouse ($RyR2^{R4496C+/-}$ mouse) are reported (Non-Patent Document 8). These findings suggest availabilities of CaMKII inhibitors in the prophylaxis and/or treatment of cardiac diseases including heart failure, cardiac hypertrophy, myocardial infarction and cardiac arrhythmia.

Recently, CaMKII exacerbating action on growth or metastasis of a certain type of cancer is suggested (Non-Patent Document 9). In addition, therapeutic effect on acute renal failure, intimal hypertrophy, hepatic fibrosis, stroke, pain, rheumatoid arthritis and the like by CaMKII inhibition are also indicated (Non-Patent Documents 10-15).

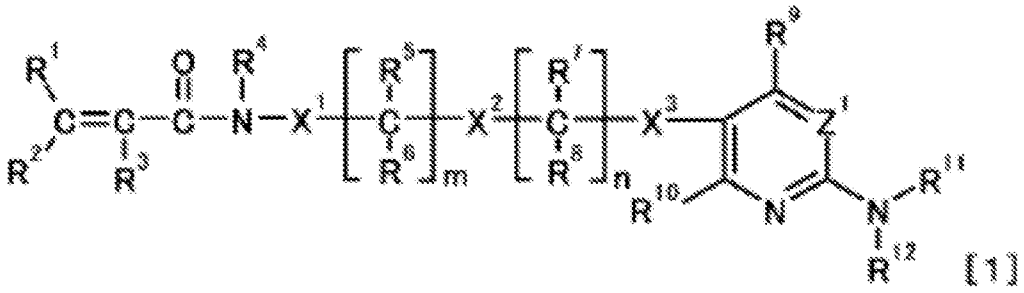
However, genetic methods achieve only deficiency of protein or overexpression of inhibitory protein, and they are different from a mechanism which inhibits temporarily kinase activity, and therefore, effects by kinase inhibitor cannot be always expected. In addition, inhibitors which have been already reported are not suitable for application as a medicament for a CaMKII selective inhibitor, because they have a low kinase selectivity to CaMKII, or they are not suitable

for oral administration or chronic administration.

[0003]

As a heterocyclic compound, the following compounds are known. Patent Document 1 describes that a compound represented by the following formula (I):

[0004]



[1]

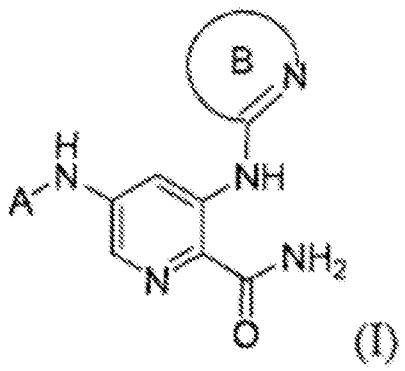
[0005]

wherein each symbol is as defined in Patent Document 1, is a FLT3 inhibitor and useful for the treatment of acute myelogenous leukemia and the like.

[0006]

Patent Document 2 describes that a compound represented by the following formula (I):

[0007]



(I)

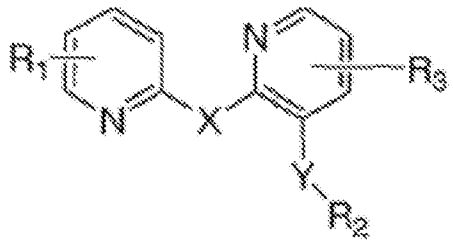
[0008]

wherein each symbol is as defined in Patent Document 2, is a Syk (Spleen tyrosine kinase) inhibitor and useful for the treatment of diseases or conditions mediated by Syk (e.g., rheumatism).

[0009]

Patent Document 3 describes that a compound represented by the following formula (I):

[0010]



[0011]

wherein each symbol is as defined in Patent Document 3, is a mGluR (metabotropic glutamate receptors)5 modulator and useful for the treatment or prophylaxis of diseases or conditions in which mGluR5 is involved (e.g., pain disorder, anxiety, depression, Alzheimer's disease, Parkinson's disease, etc.).

[0012]

Patent Document 4 describes that a compound represented by the following formula (I):

[0013]

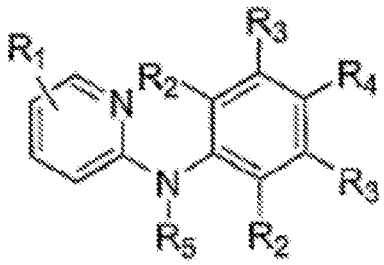
[0014]

wherein each symbol is as defined in Patent Document 4, is a kinase inhibitor (particularly an inhibitor of kinase domain in VEGF receptor (VEGF receptor tyrosine kinase inhibitor)) and useful for the treatment of vascular abnormality, tumor, diabetic retinopathy, rheumatism, endometriosis, psoriasis and the like.

[0015]

Patent Document 5 describes that a compound represented by the following formula (I):

[0016]



[0017]

wherein each symbol is as defined in Patent Document 5, is a kinase (p38 kinase, etc.) inhibitor and useful for reduction of ischemic cell death (particularly reduction of traumatic neuronalcell death).

Document List

Patent Document

[0018]

Patent Document 1: WO 2013/157540
Patent Document 2: WO 2013/052394
Patent Document 3: WO 2005/021529
Patent Document 4: WO 2002/024681
Patent Document 5: WO 2002/011724

Non-Patent Document

[0019]

Non-Patent Document 1: European Journal of Heart Failure, vol.16, p.1292-1300
Non-Patent Document 2: Circulation Research, vol.84, p.713-721
Non-Patent Document 3: Molecular Endocrinology, vol.17, p.183-192
Non-Patent Document 4: Circulation Research, vol.92, p.912-919
Non-Patent Document 5: Proceedings of the National Academy of Sciences, vol.106, p.2342-2347
Non-Patent Document 6: Circulation Research, vol.112, p.935-944
Non-Patent Document 7: Nature, vol.502, p.372-376
Non-Patent Document 8: Journal of Molecular and Cellular Cardiology, vol.50, p.214-222
Non-Patent Document 9: Oncotarget, vol.20, p.11725-11734

Non-Patent Document 10: Arterioscler Thromb Vasc Biol, vol.28, p.441-447
Non-Patent Document 11: Cell Calcium, vol.45, p.284-292
Non-Patent Document 12: J Clin Invest, vol.119, p.2925-2941
Non-Patent Document 13: J Biol Chem, vol.285, p.20675-20682
Non-Patent Document 14: J Pharmacol Exp Ther, vol.325, p.267-275
Non-Patent Document 15: BMC Musculoskelet Disord, vol.30, p.61

Summary of the Invention

Problems to be Solved by the Invention

[0020]

An object of the present invention is to provide a compound having a CaMKII inhibitory action, which is expected to be useful as an agent for the prophylaxis or treatment of cardiac diseases (particularly catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure, fatal arrhythmia) and the like.

Means of Solving the Problems

[0021]

The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that the compounds mentioned below have a CaMKII inhibitory action, and therefore, is expected to be useful as an agent for the prophylaxis or treatment of cardiac diseases (particularly catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure, fatal arrhythmia) and the like, which resulted in the completion of the present invention.

[0022]

Accordingly, the present invention provides the following.

[1] A compound selected from the group consisting of (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-

yl)benzonitrile, or a salt thereof;
2-(((S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
(S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(3,3,3-trifluoropropyl)-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;
(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(2-hydroxy-2-methylpropyl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(2,2,2-trifluoroethoxy)-1-(2-(3,3,3-trifluoropropyl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
4-(2-((1-((1r,4r)-4-(1-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)-2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)benzonitrile, or a salt thereof;
2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-

azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1r,4r)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1S,4r)-4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((2S,6R)-2,6-dimethylmorpholino)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropyl-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropyl-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-(3-methoxy-3-methylazetidin-1-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(1,1-difluoropropyl)-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

(S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;

(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-(2-(3,3,3-trifluoropropyl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof; and

5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-(oxetan-3-yloxy)-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof (hereinafter sometimes collectively to be referred to as "Compound A").

[0023]

[2] A medicament comprising the compound or salt of the above-mentioned [1].

[3] The medicament of the above-mentioned [2], which is a calcium/calmodulin-dependent protein kinase II inhibitor.

[4] The medicament of the above-mentioned [2], which is an agent for the prophylaxis or treatment of cardiac diseases.

[5] The medicament of the above-mentioned [4], wherein the

cardiac disease is selected from catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure and fatal arrhythmia.

[0024]

[6] The compound or salt of the above-mentioned [1] for use in the prophylaxis or treatment of cardiac diseases.

[7] The compound or salt of the above-mentioned [6], wherein the cardiac disease is selected from catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure and fatal arrhythmia.

[0025]

[8] A method of inhibiting calcium/calmodulin-dependent protein kinase II in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1] to the mammal.

[9] A method for the prophylaxis or treatment of cardiac diseases in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1] to the mammal.

[10] The method of the above-mentioned [9], wherein the cardiac disease is selected from catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure and fatal arrhythmia.

[0026]

[11] Use of the compound or salt of the above-mentioned [1] for the production of an agent for the prophylaxis or treatment of cardiac diseases.

[12] The use of the above-mentioned [11], wherein the cardiac disease is selected from catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure and fatal arrhythmia.

Effect of the Invention

[0027]

According to the present invention, a compound having a superior CaMKII inhibitory action, which is expected to be

useful as an agent for the prophylaxis or treatment of cardiac diseases (particularly catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure, fatal arrhythmia) and the like can be provided.

[0028]

(Detailed Description of the Invention)

[0029]

When Compound A is a salt, examples of the salt include metal salts, ammonium salts, salts with organic base, salts with inorganic acid, salts with organic acid, and salts with basic or acidic amino acid. Preferable examples of the metal salt include alkali metal salts such as sodium salts, potassium salts and the like; alkali earth metal salts such as calcium can be produce salts, magnesium salts, barium salts and the like; and aluminum salts. Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salts with basic amino acid include salts with arginine, lysine, ornithine and the like. Preferable examples of the salt with acidic amino acid include salts with aspartic acid, glutamic acid and the like. Among them, a pharmaceutically acceptable salt is preferable. For example, when a compound has an acidic functional group, examples of the salt include inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal salts (e.g., calcium

salt, magnesium salt etc.) and the like, ammonium salt etc., and when a compound has a basic functional group, examples of the salt include salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, and salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

When Compound A contains isomers such as tautomers, optical isomers, stereoisomers, position isomers and rotational isomers, any of isomers or mixture are also encompassed in Compound A. Further, when Compound A contains an optical isomer, the optical isomer separated from the racemate is encompassed in Compound A.

Compound A can be obtained in the crystal form. Either single crystalline form or crystalline mixture can be encompassed in Compound A.

Compound A can be a pharmaceutically acceptable co-crystal or a co-crystal salt. The co-crystal or co-crystal salt as used herein means a crystalline material composed of two or more unique solids at room temperature, each of which has distinctive physical characteristics such as structure, melting point, and heats of fusion, hygroscopicity, solubility, and stability. A co-crystal or a co-crystal salt can be produced according to co-crystallization method known per se.

Compound A may be a solvate (e.g., a hydrate) or a non-solvate and both are encompassed in Compound A.

Compounds labeled with or substituted by isotopes (e.g., ^{2}H, ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{35}S, ^{125}I, etc.) are also encompassed in Compound A. The compound labeled with or substituted by isotopes can be used as, for example, a tracer used for Positron Emission Tomography (PET) (PET tracer), and are expected to be useful in the field of medical diagnosis and the like.

[0030]

Compound A can be produced according to the methods described in the below-mentioned Examples.

[0031]

The starting compound and/or production intermediate for Compound A may form a salt. While the salt is not particularly limited as long as the reaction can be performed, examples thereof include those similar to the salts optionally formed by Compound A and the like, and the like.

As for the configurational isomers (E, Z forms) of Compound A, they can be isolated and purified when isomerization occurs, for example, according to a conventional separation means such as extraction, recrystallization, distillation, chromatography and the like to obtain a pure compound. In addition, the corresponding pure isomer can also be obtained by isomerizing a double bond using heating, an acid catalyst, a transition metal complex, a metal catalyst, a radical catalyst, light irradiation, a strong base catalyst and the like, according to the method described in Shin Jikken Kagaku Kouza 14 (The Chemical Society of Japan ed.), pages 251 to 253, 4th Edition Jikken Kagaku Kouza 19 (The Chemical Society of Japan ed.), pages 273 to 274 or a method analogous thereto.

[0032]

Compound A contains a stereoisomer depending on the kind of a substituent, and each stereoisomer and a mixture thereof are encompassed in the present invention.

Compound A may be a hydrate or a non-hydrate.

When desired, Compound A can be synthesized by performing deprotection reaction, acylation reaction, alkylation reaction, hydrogenation reaction, oxidation reaction, reduction reaction, reaction of carbon chain extension, halogenation reaction, substituent exchange reaction, coupling reaction, reductive amination, nucleophilic addition reaction by a carbo anion, Grignard reagent and deoxofluorination reaction singly or two or more thereof in combination.

When the objective product is obtained as a free form by the above-mentioned reaction, it can be converted to a salt according to a conventional method, or when the objective product is obtained as a salt, it can be converted to a free form or other salt according to a conventional method. The thus-obtained Compound A can also be isolated and purified from a reaction mixture according to a known method such as phase transfer, concentration, solvent extraction, distillation, crystallization, recrystallization, chromatography and the like.

When Compound A contains a configurational isomer, a diastereomer, a conformer and the like, each can be isolated according to the above-mentioned separation and purification methods, if desired. In addition, when Compound A is racemic, d-form and l-form can be isolated according to a conventional optical resolution.

[0033]

The thus-obtained Compound A, other reaction intermediate therefor and starting compounds thereof can be isolated and purified from a reaction mixture according to a method known per se, for example, extraction, concentration, neutralization, filtration, distillation, recrystallization, column chromatography, thin layer chromatography, preparative high performance liquid chromatography (preparative HPLC), moderate-pressure preparative liquid chromatography (moderate-pressure preparative LC) and the like.

[0034]

A salt of Compound A can be produced according to a method known per se. For example, when Compound A is a basic compound, it can be produced by adding an inorganic acid or organic acid, or when Compound A is an acidic compound, by adding an organic base or inorganic base.

When Compound A contains an optical isomer, each optical isomer and a mixture thereof are encompassed in the scope of the present invention, and these isomers can be subjected to

optical resolution or can be produced respectively, according to a method known per se, if desired.

When Compound A contains a configurational isomer, a diastereomer, a conformer and the like, each can be isolated according to the above-mentioned separation and purification methods, if desired. In addition, when Compound A is racemic, S-form and R-form can be isolated according to a conventional optical resolution.

When Compound A contains a stereoisomer, each isomer and a mixture thereof are encompassed in the present invention.

[0035]

Compound A may be a prodrug. A prodrug of Compound A invention means a compound which is converted to Compound A with a reaction due to an enzyme, an gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to Compound A with oxidation, reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to Compound A by hydrolysis etc. due to gastric acid, etc.

[0036]

A prodrug for Compound A may be a compound obtained by subjecting an amino group in Compound A to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in Compound A to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation, etc.); a compound obtained by subjecting a hydroxy group in Compound A to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy group in Compound A to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation, etc.); a compound obtained by subjecting a carboxyl group in Compound A to an esterification or amidation (e.g., a compound

obtained by subjecting a carboxyl group in Compound A to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation, etc.) and the like. Any of these compounds can be produced from Compound A by a method known per se. The prodrug of Compound A may be a compound that converts to Compound A under physiological conditions as described in Development of Pharmaceutical Products, vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

[0037]

Compound A or a prodrug thereof (to be abbreviated as the compound of the present invention) is superior in vivo kinetics (e.g., plasma drug half-life, intracerebral transferability, metabolic stability), shows low toxicity (e.g., more superior as a medicament in terms of acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, drug interaction, carcinogenicity etc.). The compound of the present invention is directly used as a medicament or a pharmaceutical composition mixed with a pharmaceutically acceptable carrier or the like to be orally or parenterally administered to mammals (e.g., humans, monkeys, cows, horses, pigs, mice, rats, hamsters, rabbits, cats, dogs, sheep and goats) in safety. Examples of the "parenteral" include intravenous, intramuscular, subcutaneous, intra-organ, intranasal, intradermal, instillation, intracerebral, intrarectal, intravaginal, intraperitoneal and intratumor administrations, administration to the vicinity of tumor etc. and direct administration to the lesion.

[0038]

Since the compound of the present invention has a superior CaMKII inhibitory action, it is expected to be useful for the prophylaxis or treatment of, for example,

cardiac diseases (cardiac hypertrophy, acute heart failure and chronic heart failure including congestive heart failure, cardiomyopathy, angina, myocarditis, atrial/ventricular arrhythmia, tachycardia, myocardial infarction, etc.), myocardial ischemia, venous insufficiency, post-myocardial infarction transition to heart failure, hypertension, cor pulmonale, arteriosclerosis including atherosclerosis (aneurysm, coronary arterial sclerosis, cerebral arterial sclerosis, peripheral arterial sclerosis, etc.), vascular thickening, vascular thickening/occlusion and organ damages after intervention (percutaneous coronary angioplasty, stent placement, coronary angioscopy, intravascular ultrasound, coronary thrombolytic therapy, etc.), vascular reocclusion/restenosis after bypass surgery, cardiac hypofunction after artificial heart lung surgery, respiratory diseases (cold syndrome, pneumonia, asthma, pulmonary hypertension, pulmonary thrombus/pulmonary embolism, etc.), bone disorders (nonmetabolic bone disorders such as bone fracture, refracture, bone malformation/spondylosis deformans, osteosarcoma, myeloma, dysostosis and scoliosis, bone defect, osteoporosis, osteomalacia, rickets, osteitis fibrosis, renal osteodystrophy, Paget's disease of bone, myelitis with rigidity, chronic rheumatoid arthritis, gonarthrosis and articular tissue destruction in similar disorders thereof, etc.), inflammatory diseases (diabetic complication such as retinopathy, nephropathy, nerve damage, macroangiopathy etc.; arthritis such as chronic rheumatoid arthritis, osteoarthritis, rheumatoid myelitis, periostitis etc.; inflammation after surgery/trauma; reduction of swelling; pharyngitis; cystitis; pneumonia; atopic dermatitis; inflammatory enteric diseases such as Crohn's disease, ulcerative colitis etc.; meningitis; inflammatory eye diseases; inflammatory pulmonary diseases such as pneumonia, silicosis, pulmonary sarcoidosis, pulmonary tuberculosis etc, and the like), allergic diseases (allergic rhinitis, conjunctivitis, gastrointestinal allergy, pollen

allergy, anaphylaxis, etc.), drug dependence, neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, AIDS encephalopathy, etc.), central nervous system damage (disorders such as cerebral hemorrhage and cerebral infarction and aftereffects and complications thereof, head injury, spinal damage, cerebral edema, sensory dysfunction, sensory abnormality, autonomic dysfunction, abnormal autonomic function, multiple sclerosis etc.), dementia, disturbed memory, disturbed consciousness, amnesia, anxiety symptoms, nervous symptoms, unpleasant condition, mental disorders (depression, epilepsy, alcohol dependency, etc.), ischemic peripheral circulatory disorder, deep-vein thrombosis, occlusive peripheral circulatory disorder, arteriosclerosis obliterans (ASO), occlusive thromboangiitis, diabetes (type 1 diabetes, type 2 diabetes, pregnancy diabetes etc.), diabetic complications (nerve damage, nephropathy, retinopathy, cataract, macroangiopathy, osteopenia, diabetic hyperosmolar diabetic coma, infectious diseases, diabetic gangrene, xerostomia, deterioration in hearing, cerebrovascular damage, peripheral circulatory disorder, etc.), urinary incontinence, metabolic/nutritional disorders (obesity, hyperlipidemia, hypercholesterolemia, diabetes, impaired glucose tolerance, hyperuricemia, hyperkalemia, hypernatremia etc.), metabolic syndrome, vesceral obesity syndrome, male or female sexual dysfunction and the like, and
for the prophylaxis or treatment of dysgeusia, smell disturbance, abnormal circadian rhythm of blood pressure, cerebrovascular damage (asymptomatic cerebrovascular damage, transient cerebral ischemia attack, stroke, cerebrovascular dementia, hypertensive encephalopathy, cerebral infarction, etc.), cerebral edema, cerebral circulatory disturbance, recurrence and aftereffects of cerebrovascular damages (neurological symptoms, mental symptoms, subjective symptoms, impairment of activities of daily living, etc.), kidney diseases (nephritis, glomerulonephritis, glomerulosclerosis,

renal failure, thrombotic microangiopathy, diabetic nephropathy, nephrotic syndrome, hypertensive nephrosclerosis, complications of dialysis, organ damage including nephropathy by irradiation, etc.), erythrocytosis/hypertension/organ damage/vascular thickening after transplantation、rejection after transplantation, ocular disorders (glaucoma, ocular hypertension, etc.), thrombosis, multiple organ failure, endothelial dysfunction, hypertensive tinnitus, other circulatory diseases (ischemic cerebral circulatory disturbance, Raynaud's disease, Buerger's disease, etc.), chronic occlusive pulmonary diseases, interstitial pneumonia, carinii pneumonia, connective tissue disorders (e.g., systemic erythematosus, scleroderma, polyarteritis, etc.), liver disorders (hepatitis and cirrhosis including chronic types, etc.), portal hypertension, digestive disorders (gastritis, gastric ulcer, gastric cancer, disorder after gastric surgery, poor digestion, esophageal ulcer, pancreatitis, colon polyp, cholelithiasis, hemorrhoidal problem, esophageal and gastric variceal rupture, etc.), hematological/hematopoietic disorders (erythrocytosis, vascular purpura, autoimmune hemolytic anemia, disseminated intravascular coagulation syndrome, multiple myelosis, etc.), solid tumor, tumors (malignant melanoma, malignant lymphoma, digestive organs (e.g., stomach, intestine, etc.) cancers, etc.), cancers and cachexia associated therewith, cancer metastases, endocrine disorders (Addison's disease, Cushing's syndrome, pheochromocytoma, primary aldosteronism, etc.), Creutzfeldt-Jakob disease, urological/male genital diseases (cystitis, prostatic enlargement, prostate cancer, sexually transmitted diseases, etc.), gynecological disorders (menopausal disorders, pregnancy toxemia, endometriosis, uterine fibroid, ovarian diseases, mammary gland diseases, sexually transmitted diseases, etc.), diseases caused by environmental/occupational factor (e.g., radiation damage, damage from ultraviolet/infrared/laser beam,

altitude sickness etc.), infectious diseases (viral infectious diseases of, for example, cytomegalovirus, influenza virus and herpesvirus, rickettsial infectious diseases, bacterial infectious diseases, etc.), toxemia (septicemia, septic shock, endotoxic shock, gram-negative septicemia, toxin shock syndrome, etc.), ear nose throat diseases (Ménière's disease, tinnitus, dysgeusia, vertigo, balance disorder, deglutition disorder etc.), cutaneous diseases (keloid, hemangioma, psoriasis, etc.), dialysis hypotension, myasthenia gravis, systemic diseases such as chronic fatigue syndrome, and the like, particularly cardiac diseases (particularly catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure, fatal arrhythmia) and the like,
in animals, particularly mammals (e.g., humans, monkeys, cats, pigs, horses, bovines, mice, rats, guinea pigs, dogs, rabbits etc.).

Herein, the concept of prophylaxis of cardiac diseases include treatment of prognosis of myocardial infarction, angina attack, cardiac bypass surgery, thrombolytic therapy, coronary revascularization and the like, and the concept of treatment of cardiac diseases include suppress of progress or severity of heart failure (including both contractile failure HFrEF, and heart failure HFpEF with maintained ejection fraction), and maintenance of cardiac function when performing non-drug therapies (e.g., an implantable defibrillator, resection of cardiac sympathetic nerve, catheter ablation, cardiac pacemaker, intra aortic balloon pumping, auxiliary artificial heart, Batista operation, cell transplantation, gene therapy, heart transplantation and the like) for severe heart failure/arrhythmia, and the like. When the compound of the present invention is applied to prophylaxis or treatment of heart failure, improvement of heart contractility or atonicity is expected to be achieved by short-time administration, without side effects such as pressure decrease, tachycardia,

reduced renal blood flow and the like, regardless of differences in causative diseases such as ischemic cardiac disease, cardiomyopathy, hypertension and the like and symptoms such as contractile failure, diastolic failure and the like. Moreover, long-term improvement of prognosis (survival rate, readmission rate, cardiac event rate etc.) is expected to be achieved, in addition to short-term improvement of cardiac function. When the compound of the present invention is applied to prophylaxis or treatment of arrhythmia, improvement or remission of the symptom is expected to be achieved, regardless of differences in etiology and atrial/ventricular. In addition, long-term improvement of prognosis (survival rate, readmission rate, cardiac event rate etc.) is expected to be achieved.

[0039]

While the dose of the compound of the present invention varies depending on the administration route, symptom and the like, when, for example, the compound is orally administered to a patient with cardiac disease (adult, body weight 40 – 80 kg, for example, 60 kg), it is, for example, 0.001 – 1000 mg/kg body weight/day, preferably 0.01 – 100 mg/kg body weight/day, more preferably 0.1 – 10 mg/kg body weight/day. This amount can be administered in 1 to 3 portions per day.

[0040]

A medicament containing the compound of the present invention can be used alone or as a pharmaceutical composition containing the compound of the present invention and a pharmaceutically acceptable carrier according to a method known per se as a production method of a pharmaceutical preparation (e.g., the method described in the Japanese Pharmacopoeia etc.). A medicament containing the compound of the present invention can be safely administered in the form of, for example, tablet (including sugar-coated tablet, film-coated tablet, sublingual tablet, orally disintegrating tablet, buccal and the like), pill, powder, granule, capsule (including soft

capsule, microcapsule), troche, syrup, liquid, emulsion, suspension, release control preparation (e.g., immediate-release preparation, sustained-release preparation, sustained-release microcapsule), aerosol, film (e.g., orally disintegrating film, oral mucosa-adhesive film), injection (e.g., subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection), drip infusion, transdermal absorption type preparation, ointment, lotion, adhesive preparation, suppository (e.g., rectal suppository, vaginal suppository), pellet, nasal preparation, pulmonary preparation (inhalant), eye drop and the like, orally or parenterally (e.g., intravenous, intramuscular, subcutaneous, intraorgan, intranasal, intradermal, instillation, intracerebral, intrarectal, intravaginal, intraperitoneal administrations, and administration to the lesion).

[0041]

As the aforementioned "pharmaceutically acceptable carrier", various organic or inorganic carriers conventionally used as preparation materials (starting materials) can be used. For example, excipient, lubricant, binder, disintegrant and the like are used for solid preparations, and solvent, solubilizing agent, suspending agent, isotonicity agent, buffer, soothing agent and the like are used for liquid preparations. Where necessary, preparation additives such as preservative, antioxidant, colorant, sweetening agent and the like can also be used.

Examples of the excipient include lactose, sucrose, D-mannitol, starch, corn starch, crystalline cellulose, light anhydrous silicic acid and the like.

Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Examples of the binding agent include crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose,

polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, carboxymethylcellulose sodium and the like.

Examples of the disintegrant include starch, carboxymethylcellulose, carboxymethylcellulose calcium, sodium carboxymethyl starch, L-hydroxypropylcellulose and the like.

Examples of the solvent include water for injection, alcohol, propylene glycol, Macrogol, sesame oil, corn oil, olive oil and the like.

Examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like. Examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride, glycerin monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; and the like.

Examples of the isotonic agent include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol and the like.

Examples of the buffering agent include buffer solutions such as phosphates, acetates, carbonates, citrates and the like.

Examples of the soothing agent include benzyl alcohol and the like.

Examples of the preservative include p-oxybenzoates, chlorobutanol, benzyl alcohol, phenylethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Examples of the antioxidant include sulfite, ascorbic acid, α-tocopherol and the like.

[0042]

While the pharmaceutical composition varies according to the dosage form, administration method, carrier and the like,

it can be produced according to a conventional method by adding the compound of the present invention in a proportion of generally 0.01 - 100%(w/w), preferably 0.1 - 95%(w/w), of the total amount of the preparation.

[0043]

When the compound of the present invention is applied to each of the above-mentioned diseases, it can be used in appropriate combination with a pharmaceutical agent (hereinafter to be abbreviated as a concomitant drug) or a treatment method generally employed for such diseases. For heart failure, for example, it can be used concurrently with angiotensin converting enzyme (ACE) inhibitors (e.g., alacepril, captopril, cilazapril, delapril, enalapril, lisinopril, temocapril, trandolapril, quinapril, imidapril, benazepril, perendopril and the like), angiotensin II receptor antagonists (e.g., losartan, candesartan cillexetil, valsartan, termisartan, irbesartan, forasartan and the like), angiotensin II receptor antagonist/NEP inhibitor combination agent (entresto), β receptor antagonists (e.g., propranolol, nadolol, timolol, nipradilol, bunitorolol, indenolol, penbutolol, carteolol, carvedilol, pindolol, acebutolol, atenolol, bisoprolol, metoprolol, labetalol, amosulalol, arotinolol and the like), Ca antagonists (e.g., manidipine, nicardipine, nilvadipine, nisoldipine, nitrendipine, benidipine, amlodipine, aranidipine and the like), diuretics (e.g., thiazide diuretics such as benzylhydrochlorothiazide, cyclopentiazide, ethiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, penfluthiazide, polythiazide, trichlormethiazide and the like; loop diuretics such as chlorthalidone, clofenamide, indapamide, mefruside, meticrane, sotolazone, tribamide, quinetazone, metolazone, furosemide, mefruside and the like; potassium retention diuretics such as spironolactone, triamterene and the like; and the like), digitalis preparations (e.g., digitoxin, digoxin, methyldigoxin, lanatoside C, proscillaridin and the like), ANP or BNP preparations, Ca sensitizers (e.g.,

pimobendan and the like), anticoagulants (e.g., warfarin, sodium citrate, activated protein C, tissue factor pathway inhibitor, antithrombin III, dalteparin sodium, aragatroban, gabexate, sodium ozagrel, ethyl icosapentate, beraprost sodium, alprostadil, pentoxifyline, tisokinase, streptokinase and the like), antiarrhythmic drugs (e.g., sodium channel blockers such as quinidine, procainamide, disopyramide, ajmaline, cibenzoline, lidocain, diphenylhydantoin, mexiletine, propafenone, flecainide, pilsicainide, phenytoin and the like; potassium channel blockers such as amiodarone and the like; calcium channel blockers such as verapamil, diltiazem and the like; and the like), PDE inhibitors (e.g., amrinone, milrinone, olprinone hydrochloride and the like), therapeutic drugs for diabetes (e.g., sulfonylureas such as tolbutamide, chlorpropamide, glyclopyramide, acetohexamide, tolazamide, glibenclamide, glybuzole and the like; biguanides such as metformin hydrochloride, buformin hydrochloride and the like; α-glucosidase inhibitors such as voglibose, acarbose and the like, insulin sensitizers such as pioglitazone, troglitazone and the like; SGLT2 inhibitors such as ipragliflozin, dapagliflozin, ruseogurifurojin, tofogliflozin, canagliflozin, empagliflozin and the like; insulin, glucagon; therapeutic drugs for diabetic complications such as epalrestat and the like; and the like), anti-obesity drugs and the like, and is also applicable when an implantable artificial heart, an implantable defibrillator, a ventricular pacing, Batista operation, heart transplantation or cell transplantation is performed. In addition, for arrhythmia, for example, it can be used concurrently with other antiarrhythmic drugs (e.g., sodium channel blockers such as flecainide, quinidine, procainamide, disopyramide, ajmaline, cibenzoline, lidocain, diphenylhydantoin, mexiletine, propafenone, pilsicainide, phenytoin and the like; potassium channel blockers such as amiodarone and the like; calcium channel blockers such as verapamil, diltiazem and the like, and the like) and β receptor

antagonists, non-drug therapies (e.g., an implantable defibrillator, resection of cardiac sympathetic nerve, catheter ablation, cardiac pacemaker and the like). In addition, after acute myocardial infarction or during myocardial infarction prognosis, for example, the compound can be used in combination with antithrombotics (e.g., anticoagulants such as heparin sodium, heparin calcium, warfarin and the like; thrombolytic agents such as urokinase and the like; anti-platelet drugs such as aspirin, sulfinpyrazone (anturan), dipyridamole (persantin), ticropidine (panaldine), cilostazol (pletal), clopidogrel and the like; and the like), angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, β receptor antagonists, therapeutic drugs for diabetes, therapeutic drugs for hyperlipidemia (e.g., HMG-CoA reductase inhibitors such as pravastatine, fluvastatine, cerivastatine, atorvastatine and the like; fibrate drugs such as sinfibrate, clofibrate aluminum, clinofibrate, fenofibrate and the like; and the like), coronary vessel reconstructive surgery such as PTCA, CABG and the like; and the like. Furthermore, in chronic rheumatoid arthritis, for example, the compound can be used in combination with non-steroidal antiinflammatory agents (e.g., acetaminophen, phenacetin, ethenzamide, sulpyrine, antipyrine, migrenine, aspirin, mefenamic acid, flufenamic acid, diclofenac sodium, loxoprofen sodium, phenylbutazone, indomethacin, ibuprofen, ketoprofen, naproxen, oxaprozin, flurbiprofen, fenbufen, pranoprofen, floctafenine, epirizole, tiaramide hydrochloride, zaltoprofen, gabexate mesilate, camostat mesilate, ulinastatine, colchicine, probenecid, sulfinpyrazone, benzbromarone, allopurinol, sodium aurothiomalate, sodium hyaluronate, sodium salicylate, morphine hydrochloride, salicylic acid, atropine, scopolamine, morphine, pethidine, levorphanol, ketoprofen, naproxen, oxymorphone or a salt thereof and the like), immunomodulators or immunosuppressants (e.g., methotrexate, cyclosporine, tacrolimus, gusperimus, azathioprine, antilymphocyte serum, dried sulfonated

immunoglobulin, erythropoietin, colony stimulating factor, interleukin, interferon and the like), steroids (e.g., dexamethasone, hexestrol, methimazole, betamethasone, triamcinolone, triamcinoloneacetonide, fluocinonide, fluocinoloneacetonide, prednisolone, methylprednisolone, cortisone acetate, hydrocortisone, fluorometholone, beclometasone dipropionate, estriol and the like), p38 MAP kinase inhibitors, anti-TNF-α drugs (e.g., etanercept, infliximab, D2E7, CDP-571, PASS TNF-α, soluble TNF-α receptor, TNF-α binding protein, anti-TNF-α antibody and the like), cyclooxygenase inhibitors (e.g., salicylic acid derivatives such as celecoxib, rofecoxib, aspirin and the like, MK-663, valdecoxib, SC-57666, tiracoxib, S-2474, diclofenac, indomethacin, loxoprofen and the like) and the like.

Moreover, it is possible to use the compound of the present invention in combination with biological products (e.g.: antibody, vaccine preparation and the like) when applying to the above-mentioned respective diseases, and it is also possible to apply the compound in combination with a gene therapy and the like as a combination therapy. As antibody and vaccine preparation, for example, vaccine preparation to angiotensin II, vaccine preparation to CETP, CETP antibody, TNF α antibody, antibody to other cytokine, amiloid β vaccine preparation, type 1 diabetes vaccine (DIAPEP-277 of Peptor Ltd. and the like), anti-HIV antibody, HIV vaccine preparation and the like, antibody and vaccine preparation to cytokine, renin-angiotensin enzyme and products thereof, antibody and vaccine preparation to enzyme and protein involved in blood lipid metabolism, antibody and vaccine preparation to enzyme and protein involved in blood coagulation-fibrinolytic system, antibody and vaccine preparation to protein involved in glucose metabolism and insulin resistance and the like can be mentioned. In addition, a combined use with biological products involved in growth factors such as GH, IGF and the like is possible. As a gene therapy, for example, a treatment

method using a gene relating to cytokine, renin-angiotensin enzyme and products thereof, G protein, G protein-coupled receptor and phosphorylation enzyme thereof, a therapeutic method using a DNA decoy such as NFκB decoy and the like, a therapeutic method using antisense, a therapeutic method using a gene relating to enzyme and protein involved in blood lipid metabolism (e.g., gene relating to metabolism, excretion and absorption of cholesterol or triglyceride or HDL-cholesterol or blood phospholipid, and the like), a therapeutic method using a gene relating to enzyme and protein (e.g., growth factors such as HGF, VEGF and the like, and the like) involved in angiogenetic therapy aiming at obstruction of peripheral vessel and the like, a therapeutic method using a gene relating protein involved in glucose metabolism and insulin resistance, antisense to cytokine such as TNF-α and the like, and the like can be mentioned. In addition, it is possible to use the compound in combination with various organ regeneration methods such as heart regeneration, kidney regeneration, pancreas regeneration, blood vessel regeneration and the like, cell transplantation therapy using bone marrow cells (bone marrow mononuclear cell, bone marrow mesenchymal stem cell and the like), and artificial organs (artificial blood vessels and cardiac muscle cell sheet) using tissue engineering.

[0044]

By combining the compound of the present invention and a concomitant drug, a superior effect such as

(1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,

(2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like),

(3) the period of treatment can be set longer by selecting a concomitant drug having different action and mechanism from the

compound of the present invention,

(4) a sustained treatment effect can be designed by selecting a concomitant drug having different action and mechanism from the compound of the present invention,

(5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

[0045]

Hereinafter the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

When using the combination agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention or a pharmaceutical composition thereof and the concomitant drug or a pharmaceutical composition thereof can be administered to an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically used, and can be appropriately selected depending on an administration subject, administration route, disease, combination and the like.

The administration mode of the concomitant drug of the present invention is not particularly restricted, and it is sufficient that the compound of the present invention and the concomitant drug are combined in administration. Examples of such administration mode include the following methods:

(1) administration of a single preparation obtained by simultaneously processing the compound of the present invention and the concomitant drug, (2) simultaneous administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by the same administration route, (3) administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately

produced, by the same administration route in a staggered manner, (4) simultaneous administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by different administration routes, (5) administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by different administration routes in a staggered manner (for example, administration in the order of the compound of the present invention and the concomitant drug, or in the reverse order) and the like.

[0046]

The combination agent of the present invention exhibits low toxicity. For example, the compound of the present invention or(and) the aforementioned concomitant drug can be combined with a pharmacologically acceptable carrier according to the known method to prepare a pharmaceutical composition such as tablets (including sugar-coated tablet and film-coated tablet), powders, granules, capsules (including soft capsule), liquids, injections, suppositories, sustained-release agents, etc. These compositions can be administered safely orally or non-orally (e.g., topical, rectal, intravenous administration etc.). Injection can be administered intravenously, intramuscularly, subcutaneously, or by intraorgan administration or directly to the lesion.

Examples of the pharmacologically acceptable carriers usable for the production of a combination agent of the present invention, various organic or inorganic carrier substances conventionally used as preparation materials can be mentioned. For solid preparations, for example, excipient, lubricant, binder and disintegrant can be used. For liquid preparations, for example, solvent, solubilizing agent, suspending agent, isotonic agent, buffering agent, soothing agent and the like can be used. Where necessary, an appropriate amount of conventional preservative, antioxidant, colorant, sweetening

agent, adsorbent, wetting agent and the like can be used as appropriate.

Examples of the excipient include lactose, sucrose, D-mannitol, starch, corn starch, crystalline cellulose, light anhydrous silicic acid and the like.

Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Examples of the binding agent include crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, carboxymethylcellulose sodium and the like.

Examples of the disintegrant include starch, carboxymethylcellulose, carboxymethylcellulose calcium, sodium carboxymethyl starch, L-hydroxypropylcellulose and the like.

Examples of the solvent include water for injection, alcohol, propylene glycol, Macrogol, sesame oil, corn oil, olive oil and the like.

Examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like.

Examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride, glycerin monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; and the like.

[0047]

Examples of the isotonic agent include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol and the like.

Examples of the buffering agent include buffer solutions such as phosphates, acetates, carbonates, citrates and the

like.

Examples of the soothing agent include benzyl alcohol and the like.

Examples of the preservative include p-oxybenzoates, chlorobutanol, benzyl alcohol, phenylethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Examples of the antioxidant include sulfite, ascorbic acid, α-tocopherol and the like.

[0048]

The mixing ratio of the compound of the present invention to the concomitant drug in the combination agent of the present invention can be appropriately selected depending on an administration subject, administration route, diseases and the like.

For example, the content of the compound of the present invention in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to about 100 wt%, preferably from about 0.1 to about 50 wt%, further preferably from about 0.5 to about 20 wt%, based on the preparation.

The content of the concomitant drug in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to about 100 wt%, preferably from about 0.1 to about 50 wt%, further preferably from about 0.5 to about 20 wt%, based on the preparation.

The content of additives such as a carrier and the like in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 1 to about 99.99 wt%, preferably from about 10 to about 90 wt%, based on the preparation.

When the compound of the present invention and a concomitant drug are separately formulated into preparations, the contents thereof are similar to the above.

Examples

[0049]

The present invention is explained in detail in the following by referring to Examples, Experimental Examples and Formulation Examples, which are not to be construed as limitative, and the invention may be changed within the scope of the present invention.

In the following Examples, the "room temperature" generally means about 10°C to about 35°C. The ratios indicated for mixed solvents are volume mixing ratios, unless otherwise specified. % means wt%, unless otherwise specified.

Unless particularly specified, the elution in column chromatography in Example was performed under observation by TLC (Thin Layer Chromatography). For TLC observation, $60F_{254}$ manufactured by Merck was used as a TLC plate, and the solvent used as an elution solvent for column chromatography was used as a developing solvent. For detection, a UV detector was adopted. In silica gel column chromatography, NH means use of aminopropylsilane-bonded silica gel, and Diol means use of 3-(2,3-dihydroxypropoxy)propylsilane-bonded silica gel. In preparative HPLC (high performance liquid chromatography), C18 means use of octadecyl-bonded silica gel. The ratios indicated for elution solvents are volume mixing ratios, unless otherwise specified.

For ^1H NMR analysis, ACD/SpecManager (trade name) software and the like were used. Peaks of a hydroxy group, an amino group and the like, which having very mild protons, may not be described.

MS was measured by LC/MS. As ionization method, ESI method or APCI method was used. The data indicates actual measured value (found). Generally, molecular ion peaks are observed, and may be observed as a fragment ion. In the case of a salt, a molecular ion peak or fragment ion peak of free form is generally observed.

The unit of sample concentration (c) for optical rotation ($[\alpha]_D$) is g/100 mL.

Elemental analysis value (Anal.) was described as calculated value (Calcd) and actual measured value (Found).

The peak by powder X-RAY diffraction in Example means the peak measured using Cu Kα-ray as a source by Ultima IV (Rigaku Corporation, Japan) at room temperature. The measurement conditions are as follows.

Electric pressure/Electric current: 40 kV/50 mA

Scan speed: 6 degree/min

Scan range of 2 Theta: 2-35 degree

The crystallinity by powder X-RAY diffraction in Example was calculated by Hermans method.

In Examples, the following abbreviations are used.

mp: melting point

MS: mass spectrum

M: mol concentration

N: normality

$CDCl_3$: deuterochloroform

DMSO-d_6: deuterodimethyl sulfoxide

^1H NMR: proton nuclear magnetic resonance

LC/MS: liquid chromatograph mass spectrometer

ESI: electrospray ionization, Electron Spray Ionization

APCI: atmospheric pressure chemical ionization, atmospheric pressure chemical ionization

Boc: tert-butoxycarbonyl

AcOH: acetic acid

DME: 1,2-dimethoxyethane

IPE: diisopropyl ether

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

TFA: trifluoroacetic acid

DMSO: dimethyl sulfoxide

$Pd(PPh_3)_4$: tetrakis(triphenylphosphine)palladium(0)

$Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium(0)

$Pd(dppf)Cl_2$-CH_2Cl_2: [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)

BINAP: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

MeOH: methanol

EtOH: ethanol

n-BuOH: normal butanol

THF: tetrahydrofuran

DMF: N,N-dimethylformamide

DMA: N,N-dimethylacetoamide

NMP: methylpyrrolidone

CH_3CN: acetonitrile

[0050]

Example 1

(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0051]

A) 4-bromo-2-(((2S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)benzonitrile

To a mixture of (2S)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (6.79 g) and DMF (120 ml) was added 60% sodium hydride (2.56 g) at 0°C. The mixture was stirred at 0°C for 15 min, 4-bromo-2-fluorobenzonitrile (11.8 g) was added to the mixture, and the mixture was stirred at room temperature for 2 days. To the mixture was added water at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane). After a mixture of the obtained solid and IPE was stirred at room temperature for 1 hr, and the precipitated solid was collected by filtration to give the title compound (9.60 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (3H, d, J = 6.1 Hz), 4.52 (2H, d, J = 5.6 Hz), 5.05-5.19 (1H, m), 7.28 (1H, dd, J = 8.3, 1.7 Hz), 7.45 (1H, d, J = 1.5 Hz), 7.64 (1H, d, J = 8.2 Hz), 7.95 (1H, s), 8.46 (1H, s); MS *m/z* 306.9 $[M+1]^+$.

[0052]

B) (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile

To a mixture of 4-bromo-2-(((2S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)benzonitrile (4.00 g), (2-chloropyrimidin-5-yl)boronic acid (3.70 g) and cesium carbonate (8.47 g) in THF (50 mL) and water (10 mL) was added bis(tri-tert-butylphosphane)palladium(0) (664 mg) at room temperature. The mixture was stirred at 75°C under nitrogen atmosphere for 2 hr. The mixture was quenched with saturated aqueous ammonium chloride solution at 0°C and diluted with ethyl acetate. The mixture was filtered through Celite, and the organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was suspended in ethyl acetate (50 mL), the insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane, MeOH/ethyl acetate) and purified by silica gel column chromatography (NH, ethyl acetate/hexane, MeOH/ethyl acetate) to give the title compound (1.00 g).

MS *m/z* 341.1 $[M+1]^+$.

[0053]

C) tert-butyl 6-(methanesulfonyloxy)-2-azaspiro[3.3]heptane-2-carboxylate

To a solution of tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (30.0 g) and triethylamine (29.2 mL) in THF (600 mL) was added methanesulfonyl chloride (13.0 mL) at 0°C. The mixture was stirred at room temperature under nitrogen atmosphere for 2 hr. The mixture was quenched with water at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesuim sulfate and concentrated under reduced pressure to give the title compound (40.7 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (9H, s), 2.39-2.55 (2H, m), 2.61-2.76 (2H, m), 2.98 (3H, s), 3.93 (4H, s) 4.89 (1H, quin, J = 7.18 Hz).

[0054]

D) tert-butyl 6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate

To a solution of 4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazole (28.9 g) and tert-butyl 6-(methanesulfonyloxy)-2-azaspiro[3.3]heptane-2-carboxylate (32.9 g) in DMF (500 mL) was added cesium carbonate (92.2 g) at room temperature. The mixture was stirred at 100°C for 14 hr. The mixture was quenched with water at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesuim sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and silica gel column chromatography (ethyl acetate/hexane) to give the title compound (36.0 g).

MS *m/z* 407.2 $[M+1]^+$.

[0055]

E) 6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane

To a solution of tert-butyl 6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate (20.0 g) in toluene (200 mL) was added TFA (32.3 mL) at 0°C. The mixture was stirred at room temperature for 1 hr. After concentration to remove TFA, the mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesuim sulfate and concentrated under reduced pressure to give the title compound (15.0 g). The obtained compound was used in the next reaction without purification.

MS *m/z* 307.1 $[M+1]^+$.

[0056]

F) 6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptane

To a solution of 6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane (15.0 g) and dihydro-2H-pyran-4(3H)-one (14.6 g) in THF (150 mL) and MeOH (150 mL) was added AcOH (13.9 mL) at room temperature. The mixture was stirred at room temperature for 10 min. Sodium triacetoxyborohydride (12.4 g) was added portionwise to the mixture at 0°C. The mixture was stirred at room temperature for 1 hr. After concentration to reduce the solvent volume, the mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesuim sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (17.7 g).

MS *m/z* 391.1 $[M+1]^+$.

[0057]

G) 1-[2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl]-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-amine

A mixture of 6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptane (10.0 g) and 10% palladium-carbon (1.36 g) in MeOH (100 mL) and THF (100 mL) was stirred under normal pressure of hydrogen atmosphere at room temperature for 2 hr. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure to give the title compound (9.22 g). The obtained compound was used in the next reaction without purification.

MS *m/z* 361.3 $[M+1]^+$.

[0058]

H) (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-3-

(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

To a solution of (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (500 mg), 1-[2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl]-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-amine (184 mg), BINAP (62.7 mg) and $Pd_2(dba)_3$ (46.6 mg) in DMA (4.0 mL) was added DBU (150 µL) at room temperature. The mixture was stirred at 100°C under nitrogen atmosphere for 1 hr. The mixture was quenched with water at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and silica gel column chromatography (MeOH/ethyl acetate) to give the title compound (47.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31-1.46 (2H, m), 1.50 (3H, d, J = 6.33 Hz), 1.58-1.73 (2H, m), 2.16-2.33 (1H, m), 2.66 (4H, d, J = 7.90 Hz), 3.23-3.44 (6H, m), 3.93-4.04 (2H, m), 4.40-4.54 (3H, m), 4.65 (2H, q, J = 8.31 Hz), 4.92-5.03 (1H, m), 6.84 (1H, s), 6.90 (1H, s), 7.13 (1H, d, J = 8.07 Hz), 7.60 (1H, d, J = 7.98 Hz), 7.91 (2H, d, J = 14.49 Hz), 8.28 (1H, s), 8.56 (2H, s).

[0059]

Example 2

2-(((S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0060]

A) 1-{1,4-dioxaspiro[4.5]decan-8-yl}-4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazole

To a solution of 1,4-dioxaspiro[4.5]decan-8-yl methanesulfonate (1.50 g) and 4-nitro-5-(2,2,2-trifluoroethoxy)-1H-pyrazole (1.35 g) in DMF (29 mL) was added cesium carbonate (4.13 g) at room temperature, and the mixture

was stirred at 100°C for 15 hr. The mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (961 mg).
^{1}H NMR (300 MHz, DMSO-d_6) δ 1.58-1.88 (4H, m), 1.93-2.05 (4H, m), 3.85-3.93 (4H, m), 4.18-4.28 (1H, m), 4.98 (2H, q, J = 9.0 Hz), 8.80 (1H, s); MS *m/z* 352.1 $[M+1]^+$.

[0061]

B) 4-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]cyclohexan-1-one

To a solution of 1-{1,4-dioxaspiro[4.5]decan-8-yl}-4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazole (25 g) in THF (100 mL) was added 6 M aqueous hydrogen chloride solution (23.6 mL) at room temperature. The mixture was stirred at 50°C under nitrogen atmosphere for 14 hr. The mixture was concentrated in vacuo, the residue was diluted with water/ethyl acetate, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (11.3 g).
^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17-2.41 (6H, m), 2.53-2.64 (2H, m), 4.59-4.71 (1H, m), 5.01 (2H, q, J = 8.8 Hz), 8.88 (1H, s).

[0062]

C) 4-[(1r,4r)-4-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]cyclohexyl]morpholine

To a solution of 4-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]cyclohexan-1-one (11.5 g) and morpholine (6.51 g) in MeOH (100 mL)/AcOH (10 mL) was added 2-methylpyridine-borane (8.00 g) at room temperature. The mixture was stirred at 60°C under nitrogen atmosphere for 4 hr. 8 M Aqueous sodium hydroxide solution was added to the solution to adjust the pH of the solution to 8-9 and then concentrated in vacuo. The

mixture was diluted with water/ethyl acetate and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, MeOH/ethyl acetate) and silica gel column chromatography (MeOH/ethyl acetate) to give the title compound (5.2 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28-1.42 (2H, m), 1.67-1.82 (2H, m), 1.89-1.97 (2H, m), 2.03-2.12 (2H, m), 2.21-2.32 (1H, m), 2.44-2.48 (4H, m), 3.56 (4H, brs), 4.00-4.12 (1H, m), 4.92-5.03 (2H, m), 8.78 (1H, s); MS m/z 379.2 $[M+1]^+$.

[0063]

D) tert-butyl N-{1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl}carbamate

To a mixture of 4-[(1r,4r)-4-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]cyclohexyl]morpholine (20.0 g), 10% palladium-carbon (1.87 g) and triethylamine (13.8 g) in MeOH (400 mL) was added di-tert-butyl dicarbonate (22.9 g) at room temperature. A mixture of reaction was stirred under normal pressure of hydrogen atmosphere at room temperature for 10 hr. The catalyst was removed by filtration, and then the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (17.0 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.29-1.46 (11H, m), 1.58-1.73 (2H, m), 1.85-1.94 (2H, m), 1.97-2.05 (2H, m), 2.19-2.29 (1H, m), 2.47 (4H, brs), 3.56 (4H, brs), 3.81-3.92 (1H, m), 4.71 (2H, q, J = 8.8 Hz), 7.57-7.64 (1H, m), 8.27-8.35 (1H, m); MS m/z 449.3 $[M+1]^+$.

[0064]

E) 1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-amine hydrochloride

To a mixture of tert-butyl N-{1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl}carbamate (14.2 g) and EtOH (80 mL) was added 4 M hydrogen

chloride-ethyl acetate (11.6 g). After being stirred at room temperature for 6 hr, the mixture was concentrated in vacuo. The residue was subjected to the next step without further purification.

MS m/z 349.3 $[M+1]^+$.

[0065]

F) 2-(((S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of 1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-amine hydrochloride (1.33 g) and (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (1.30 g) in NMP (3.0 mL) was stirred at 110°C under nitrogen atmosphere for 14 hr. The mixture was diluted with ethyl acetate and extracted with 2 M aqueous hydrogen chloride solution. 8 M aqueous sodium hydroxide solution was added to the aqueous layer to adjust the pH of the solution to 9-10, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/ethyl acetate) and silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.30 g). The obtained solid was crystallized from ethyl acetate/EtOH to give the title compound (1.06 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30-1.44 (5H, m), 1.62-1.77 (2H, m), 1.87-1.97 (2H, m), 2.02-2.11 (2H, m), 2.24-2.33 (1H, m), 2.44 (4H, brs), 3.57 (4H, brs), 3.86-3.99 (1H, m), 4.51-4.61 (2H, m), 4.76 (2H, q, J = 9.1 Hz), 5.18-5.29 (1H, m), 7.37 (1H, d, J = 7.6 Hz), 7.42 (1H, s), 7.73 (1H, d, J = 7.4 Hz), 7.79 (1H, s), 7.94 (1H, s), 8.49 (1H, s), 8.79 (2H, s), 8.89 (1H, s).

[0066]

Example 3

(S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(3,3,3-trifluoropropyl)-1H-pyrazol-4-yl)pyrimidin-2-amine

[0067]

A) methyl (2S)-2-(5-bromo-2-chlorophenoxy)propanoate

To a mixture of 5-bromo-2-chlorophenol (31.0 g), methyl (2R)-2-hydroxypropanoate (31.1 g), triphenylphosphine (118 g) and THF (dry) (250 mL) was added 2.2 M diethyl (E)-diazene-1,2-dicarboxylate toluene solution (238 mL) at 0°C, and the mixture was stirred at room temperature overnight under nitrogen atmosphere. To the mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. To the obtained residue were added hexane and IPE (1:1, 200 mL), the mixture was stirred at 0°C for 20 min, and the reaction solution was concentrated. To the obtained solid were added IPE and ethyl acetate (2:1, 400 mL) and the mixture was stirred at 0°C for 30 min. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (43.9 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (3H, d, J = 6.7 Hz), 3.70 (3H, s), 5.24 (1H, q, J = 6.8 Hz), 7.18 (1H, dd, J = 8.4, 2.1 Hz), 7.26 (1H, d, J = 2.1 Hz), 7.41 (1H, d, J = 8.4 Hz).

[0068]

B) (2S)-2-(5-bromo-2-chlorophenoxy)propan-1-ol

To a mixture of methyl (2S)-2-(5-bromo-2-chlorophenoxy)propanoate (43.9 g) and MeOH (204 mL)/THF (dry) (120 mL) was added sodium tetrahydroborate (5.66 g) at 0°C. The mixture was stirred at room temperature overnight. To the mixture was added saturated aqueous ammonium chloride solution at 0°C, and the mixture was concentrated under reduced pressure. The obtained residue was extracted with ethyl

acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (40.4 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22 (3H, d, J = 6.2 Hz), 3.44-3.62 (2H, m), 4.47-4.62 (1H, m), 4.91 (1H, t, J = 5.6 Hz), 7.12 (1H, dd, J = 8.4, 2.2 Hz), 7.37 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 2.2 Hz).

[0069]

C) (2S)-2-(5-bromo-2-chlorophenoxy)propyl methanesulfonate

To a mixture of (2S)-2-(5-bromo-2-chlorophenoxy)propan-1-ol (40.4 g), triethylamine (30.8 g) and THF (dry) (200 mL) was added methanesulfonyl chloride (24.4 g) at 0°C. The mixture was stirred at room temperature for 1 hr under nitrogen atmosphere. To the mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate) to give the title compound (52.0 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (3H, d, J = 6.2 Hz), 3.21 (3H, s), 4.27-4.37 (1H, m), 4.37-4.46 (1H, m), 4.85-5.02 (1H, m), 7.18 (1H, d, J = 8.4 Hz), 7.40 (1H, d, J = 8.4 Hz), 7.49 (1H, s).

[0070]

D) 1-((2S)-2-(5-bromo-2-chlorophenoxy)propyl)-1H-tetrazole

To a mixture of (2S)-2-(5-bromo-2-chlorophenoxy)propyl methanesulfonate (52.0 g), potassium carbonate (41.8 g) and DMF (dry) (100 mL) was added 1H-tetrazole (21.2 g) at room temperature. The mixture was stirred at 80°C overnight. To the mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over

anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (26.0 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, d, J = 5.9 Hz), 4.64-4.87 (3H, m), 6.97 (1H, s), 7.09 (1H, d, J = 8.5 Hz), 7.21-7.26 (1H, m), 8.92 (1H, s); MS *m/z* 317.0 $[M+1]^+$.

[0071]

E) 1-((2S)-2-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propyl)-1H-tetrazole

To a mixture of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (12.0 g), 1-((2S)-2-(5-bromo-2-chlorophenoxy)propyl)-1H-tetrazole (10.0 g), potassium acetate (9.27 g) and DMSO (100 mL) was added $Pd(dppf)Cl_2$-CH_2Cl_2 (2.57 g) at room temperature. The mixture was stirred at 100°C for 2 hr under nitrogen atmosphere. To the mixture were added water and ethyl acetate at room temperature, the insoluble material was removed by filtration through Celite, and the filtrate was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (16.9 g). This product was subjected to the next reaction without further purification.

MS *m/z* 365.2 $[M+1]^+$.

[0072]

F) 2-chloro-5-(4-chloro-3-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)phenyl)pyrimidine

To a mixture of 1-((2S)-2-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propyl)-1H-tetrazole (12.3 g), 5-bromo-2-chloropyrimidine (9.82 g), cesium carbonate (33.1 g), DME (100 mL) and water (25 mL) was added $Pd(dppf)Cl_2$-CH_2Cl_2 (2.76 g) at room temperature. The mixture was stirred at 100°C for 5 hr under nitrogen atmosphere. To the reaction solution was added water at room temperature, and the insoluble material was removed by filtration. The filtrate

was partitioned with ethyl acetate-water, and the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.18 g).
^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (3H, d, J = 6.3 Hz), 4.76-5.00 (2H, m), 5.21 (1H, td, J = 6.6, 3.6 Hz), 7.37-7.44 (1H, m), 7.51-7.61 (2H, m), 9.08-9.16 (2H, m), 9.33-9.40 (1H, m); MS *m/z* 351.1 $[M+1]^+$

[0073]

G) (1E)-1-(dimethylamino)-6,6,6-trifluorohex-1-en-3-one

A mixture of 5,5,5-trifluoropentan-2-one (2.00 g) in (dimethoxymethyl)dimethylamine (4.7 mL) was stirred at 110°C under nitrogen atmosphere for 14 hr. The mixture was concentrated under reduced pressure to give the title compound (2.77 g). This product was subjected to the next reaction without further purification.
MS *m/z* 196.1 $[M+1]^+$.

[0074]

H) 3-(3,3,3-trifluoropropyl)-1H-pyrazole

To a mixture of (1E)-1-(dimethylamino)-6,6,6-trifluorohex-1-en-3-one (2.77 g) in n-BuOH (5.0 mL) was added hydrazine hydrate (1.5 mL) at room temperature. The mixture was stirred at 130°C for 4 hr. The mixture was concentrated under reduced pressure and coevaporated with toluene. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.00 g).
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36-2.65 (2H, m), 2.86-3.06 (2H, m), 6.17 (1H, s), 7.42-7.60 (1H, m) 9.32-11.02 (1H, m).

[0075]

I) 4-nitro-3-(3,3,3-trifluoropropyl)-1H-pyrazole

To a solution of 3-(3,3,3-trifluoropropyl)-1H-pyrazole (996 mg) in sulfuric acid (1.9 mL) was added nitric acid (1.3 mL) at 0°C dropwise. The mixture was stirred at 70°C for 14 hr. The mixture was poured into iced water at 0°C and extracted

with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (502 mg).
MS *m/z* 208.1 $[M-1]^-$.

[0076]

J) tert-butyl 6-[4-nitro-3-(3,3,3-trifluoropropyl)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate

To a solution of 4-nitro-3-(3,3,3-trifluoropropyl)-1H-pyrazole (500 mg) and tert-butyl 6-(methanesulfonyloxy)-2-azaspiro[3.3]heptane-2-carboxylate (696 mg) in DMF (10 mL) was added cesium carbonate (2.33 g) at room temperature. The mixture was stirred at 100°C for 14 hr. The mixture was quenched with water at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (800 mg).
MS *m/z* 405.2 $[M+1]^+$.

[0077]

K) tert-butyl 6-[4-amino-3-(3,3,3-trifluoropropyl)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate

A mixture of tert-butyl 6-[4-nitro-3-(3,3,3-trifluoropropyl)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate (500 mg) and 10% palladium-carbon (118 mg) in MeOH (12 mL) and THF (12 mL) was stirred at room temperature for 7 hr under normal pressure of hydrogen atmosphere. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give the title compound. This product was used without further purification next step.
MS *m/z* 375.3 $[M+1]^+$.

[0078]

L) tert-butyl 6-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(3,3,3-trifluoropropyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate

A mixture of 2-chloro-5-(4-chloro-3-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)phenyl)pyrimidine (474 mg), tert-butyl 6-[4-amino-3-(3,3,3-trifluoropropyl)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate (460 mg), $Pd_2(dba)_3$ (56.3 mg), BINAP (76.5 mg) and DBU (280 mg) in DMA (6.0 mL) was stirred at 100°C for 1 hr under argon atmosphere. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (179 mg).

MS *m/z* 589.2 $[M+1]^+$.

[0079]

M) N-(1-{2-azaspiro[3.3]heptan-6-yl}-3-(3,3,3-trifluoropropyl)-1H-pyrazol-4-yl)-5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-amine

TFA (1.44 g) was added to tert-butyl 6-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(3,3,3-trifluoropropyl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (176 mg) at 0°C. The mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure. MeOH was added to the residue, and Amberlyst® A21 was added to the basic mixture. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure to give the title compound. This product was used without further purification next step.

MS *m/z* 589.2 $[M+1]^+$.

[0080]

N) (S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(3,3,3-trifluoropropyl)-1H-pyrazol-4-yl)pyrimidin-2-amine

A mixture of N-(1-{2-azaspiro[3.3]heptan-6-yl}-3-(3,3,3-trifluoropropyl)-1H-pyrazol-4-yl)-5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-amine (128 mg), oxetan-3-one (77.8 mg) and 2-methylpyridine-borane (68.3 mg) in MeOH (2.5 mL), THF (2.5 mL) and AcOH (0.25 mL) was stirred at 60°C for 40 min. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (36.7 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.33 (3H, d, J = 6.1 Hz), 2.53-2.63 (6H, m), 2.77-2.85 (2H, m), 3.19 (2H, s), 3.29 (2H, brs), 3.62-3.69 (1H, m), 4.32 (2H, brt, J = 5.7 Hz), 4.53 (2H, t, J = 6.5 Hz), 4.62-4.70 (1H, m), 4.76-4.84 (1H, m), 4.88-4.95 (1H, m), 5.15-5.23 (1H, m), 7.26 (1H, d, J = 8.1 Hz), 7.38 (1H, s), 7.45 (1H, d, J = 8.5 Hz), 7.94 (1H, s), 8.74 (2H, s), 9.12 (1H, s), 9.37 (1H, s).

[0081]

Example 4

(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(2-hydroxy-2-methylpropyl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0082]

A) 2-methyl-1-{6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptan-2-yl}propan-2-ol

A mixture of 6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane (3.80 g), 2,2-dimethyloxirane (12 mL) and N,N-diisopropylethylamine (5.91 mL)

in THF (5.0 mL) was heated at 100°C for 3 hr under microwave irradiation. The mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and crystallized from ethyl acetate/IPE/hexane to give the title compound (1.67 g).

MS *m/z* 379.2 $[M+1]^+$.

[0083]

B) 1-{6-[4-amino-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptan-2-yl}-2-methylpropan-2-ol

A mixture of 2-methyl-1-{6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptan-2-yl}propan-2-ol (300 mg) and 10% palladium-carbon (84.1 mg) in THF (6.0 mL) and MeOH (6.0 mL) was stirred under normal pressure of hydrogen atmosphere at room temperature for 2 hr. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure to give the title compound (275 mg). This product was subjected to the next reaction without further purification.

MS *m/z* 349.1 $[M+1]^+$.

[0084]

C) (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(2-hydroxy-2-methylpropyl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

To a solution of (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (295 mg), 1-{6-[4-amino-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptan-2-yl}-2-methylpropan-2-ol (275 mg), BINAP (97.7 mg) and $Pd_2(dba)_3$ (72.2 mg) in DMA (7.0 mL) was added DBU (234 µL) at room temperature. The mixture was stirred at 100°C under nitrogen atmosphere for 2 hr. The mixture was quenched with water at 0°C and extracted with ethyl acetate. The organic

layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and silica gel column chromatography (MeOH/ethyl acetate) to give the title compound (74.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (6H, s), 1.50 (3H, d, J = 6.24 Hz), 2.48 (2H, s), 2.65 (4H, d, J = 7.80 Hz), 3.52 (4H, d, J = 12.70 Hz), 4.36-4.53 (3H, m), 4.65 (2H, q, J = 8.34 Hz), 4.90-5.07 (1H, m), 6.84 (1H, s), 6.98 (1H, s), 7.13 (1H, d, J = 8.07 Hz), 7.60 (1H, d, J = 7.98 Hz), 7.91 (2H, d, J = 15.68 Hz), 8.28 (1H, s), 8.56 (2H, s), OH was not detected.

[0085]

Example 5

(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(2,2,2-trifluoroethoxy)-1-(2-(3,3,3-trifluoropropyl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0086]

A) methyl (2S)-2-(5-bromo-2-cyanophenoxy)propanoate

To a mixture of 4-bromo-2-hydroxybenzonitrile (14.5 g), methyl (2R)-2-hydroxypropanoate (15.3 g), triphenylphosphine (57.6 g) and THF (dry) (150 mL) was added 2.2 M diethyl (E)-diazene-1,2-dicarboxylate-toluene (116 mL) at 0°C. The mixture was stirred at room temperature overnight under nitrogen atmosphere. To the mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (20.0 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.57 (3H, d, J = 6.8 Hz), 3.71 (3H, s), 5.40 (1H, q, J = 6.8 Hz), 7.35 (1H, dd, J = 8.3, 1.7 Hz), 7.47 (1H, d, J = 1.6 Hz), 7.72 (1H, d, J = 8.3 Hz).

[0087]

B) 4-bromo-2-(((2S)-1-hydroxypropan-2-yl)oxy)benzonitrile

To a mixture of methyl (2S)-2-(5-bromo-2-cyanophenoxy)propanoate (20.0 g) and THF (dry) (100 mL)/MeOH (170 mL) was added sodium tetrahydroborate (2.66 g) at 0°C, and the mixture was stirred at room temperature under nitrogen atmosphere. After being stirred for 3 hr, additional sodium tetrahydroborate (2.13 g) was added to the mixture at 0°C and the mixture was stirred at room temperature overnight. To the mixture was added saturated aqueous ammonium chloride solution at 0°C, and the mixture was concentrated under reduced pressure, and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (18.0 g). This product was subjected to the next reaction without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (3H, d, J = 6.1 Hz), 3.50-3.57 (2H, m), 4.71 (1H, sxt, J = 5.7 Hz), 4.97 (1H, t, J = 5.5 Hz), 7.28 (1H, dd, J = 8.3, 1.7 Hz), 7.60 (1H, d, J = 1.7 Hz), 7.66 (1H, d, J = 8.3 Hz).

[0088]

C) (2S)-2-(5-bromo-2-cyanophenoxy)propyl methanesulfonate

To a mixture of 4-bromo-2-(((2S)-1-hydroxypropan-2-yl)oxy)benzonitrile (32.6 g), triethylamine (25.8 g) and THF (dry) (300 mL) was added methanesulfonyl chloride (20.4 g) at 0°C. The mixture was stirred at room temperature for 2 hr under nitrogen atmosphere. To the mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate) to give the title compound (42.5 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.33 (3H, d, J = 6.2 Hz), 3.21-3.25 (3H, m), 4.31-4.40 (1H, m), 4.42-4.49 (1H, m), 5.07 (1H, quind, J = 6.2, 3.0 Hz), 7.34 (1H, dd, J = 8.3, 1.7 Hz), 7.66 (1H, d, J = 1.6 Hz), 7.71 (1H, d, J = 8.3 Hz); MS *m/z* 334.1 $[M+1]^+$.

[0089]

D) 4-bromo-2-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)benzonitrile

To a mixture of (2S)-2-(5-bromo-2-cyanophenoxy)propyl methanesulfonate (25.0 g), 1H-tetrazole (10.5 g) and DMF (dry) (100 mL) was added potassium carbonate (20.7 g) at room temperature, and the mixture was stirred at 80°C overnight. To the mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (10.3 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ1.44-1.51 (3H, m), 4.64-4.77 (1H, m), 4.79-4.89 (2H, m), 7.01 (1H, d, J = 1.6 Hz), 7.21 (1H, dd, J = 8.3, 1.7 Hz), 7.42 (1H, d, J = 8.2 Hz), 8.88-9.02 (1H, m); MS *m/z* 308.2 $[M+1]^+$.

[0090]

E) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)benzonitrile

To a mixture of 4-bromo-2-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)benzonitrile (6.30 g) and DMSO (120 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (7.79 g) and Pd(dppf)Cl_2-CH_2Cl_2 (1.67 g) at room temperature, and the mixture was stirred at 100°C for 3 hr under nitrogen atmosphere. To the reaction solution was added water at room temperature, and the insoluble material was removed by filtration. The filtrate was partitioned with ethyl acetate-water, and the organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and

concentrated under reduced pressure to give the title compound. The obtained title compound was used in the next reaction without purification.

MS *m/z* 356.3 $[M+1]^+$.

[0091]

F) (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile

A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)benzonitrile (7.26 g), 5-bromo-2-chloropyrimidine (5.93 g), $Pd(dppf)Cl_2$-CH_2Cl_2 (1.67 g), cesium carbonate (20.0 g) and DME (80 mL)/water (20 mL) was stirred at 100°C under normal pressure of nitrogen atmosphere for 5 hr. The mixture was quenched with water. The insoluble material was removed by filtration, and the filtrate was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesuim sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) and crystallized from ethyl acetate/IPE to give the title compound (2.00 g).

^1H NMR (300 MHz, DMSO-d_6) δ 1.37 (3H, d, J = 6.0 Hz), 4.79-5.03 (2H, m), 5.28-5.45 (1H, m), 7.55 (1H, d, J = 8.3 Hz), 7.66 (1H, s), 7.89 (1H, d, J = 8.0 Hz), 9.14-9.24 (2H, m), 9.35 (1H, s);

MS *m/z* 342.1 $[M+1]^+$.

[0092]

G) tert-butyl 6-[4-amino-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate

A mixture of tert-butyl 6-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate (21.0 g) and 10% palladium-carbon (1.12 g) in ethyl acetate (100 mL)/EtOH (100 mL) was stirred under normal pressure of hydrogen atmosphere at room temperature for 10 hr. The catalyst was removed by filtration, and then the filtrate was concentrated in vacuo. The residue was purified by column

chromatography (NH, ethyl acetate/hexane) to give the title compound (15.6 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (9H, s), 2.39-2.49 (4H, m), 3.48 (2H, s), 3.82 (2H, brs), 3.90 (2H, brs), 4.38 (1H, quin, J = 7.9 Hz), 4.71 (2H, q, J = 9.1 Hz), 7.04 (1 H, s); MS *m/z* 377.2 $[M+1]^+$.

[0093]

H) tert-butyl 6-(4-{[5-(4-cyano-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate

To a mixture of (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (2.01 g), tert-butyl 6-[4-amino-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate (1.85 g), BINAP (611 mg) and $Pd_2(dba)_3$ (449 mg) in DMA (40 mL) was added DBU (1.46 mL) at room temperature. The mixture was stirred at 100°C under nitrogen atmosphere for 2 hr. The mixture was quenched with water at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.17 g).

MS *m/z* 682.3 $[M+1]^+$.

[0094]

I) 4-{2-[(1-{2-azaspiro[3.3]heptan-6-yl}-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile

To a solution of tert-butyl 6-(4-{[5-(4-cyano-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (1.17 g) in toluene (16 mL) was added TFA (4.0 mL) at 0°C. The mixture was stirred at 0°C

for 1 hr. The mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound. The obtained oil was used for next reaction without purification.

MS *m/z* 582.2 $[M+1]^+$.

[0095]

J) (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(2,2,2-trifluoroethoxy)-1-(2-(3,3,3-trifluoropropyl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

To a mixture of 4-{2-[(1-{2-azaspiro[3.3]heptan-6-yl}-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (100 mg) and triethylamine (71.4 µL) in CH_3CN (3.0 mL) was added 1,1,1-trifluoro-3-iodopropane (19.3 µL) at 0°C. The mixture was stirred at 50°C for 14 hr. The mixture was quenched with water at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (33.0 mg).

^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (3H, d, J = 6.05 Hz), 2.06-2.25 (2H, m), 2.57-2.71 (6H, m), 3.30 (4H, d, J = 14.58 Hz), 4.46 (1H, quin, J = 8.05 Hz), 4.58-4.79 (3H, m), 4.82-5.04 (2H, m), 6.86 (1H, s), 6.96 (1H, s), 7.17 (1H, d, J = 7.98 Hz), 7.63 (1H, d, J = 7.98 Hz), 7.89 (1H, s), 8.56 (2H, s), 8.96 (1H, s).

[0096]

Example 6

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-(2,2,2-

trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0097]

A) 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-amine

A mixture of 1-{1,4-dioxaspiro[4.5]decan-8-yl}-4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazole (4.70 g) and 10% palladium-carbon (430 mg) in EtOH (40 mL) and ethyl acetate (40 mL) was stirred under normal pressure of hydrogen atmosphere at room temperature for 15 hr. The catalyst was removed by filtration, and then the filtrate was concentrated under reduced pressure to give the title compound (4.00 g). This product was subjected to the next reaction without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56-1.89 (8H, m), 3.41 (2H, brs), 3.82-3.94 (5H, m), 4.69 (2 H, q, J = 9.1 Hz), 7.02 (1 H, s); MS *m/z* 322.1 $[M+1]^+$.

[0098]

B) 4-{2-[(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile

A mixture of 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-amine (500 mg), (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (529 mg), BINAP (193 mg), DBU (353 mg) and $Pd_2(dba)_3$ (141 mg) in DMA (10 mL) was heated at 100°C for 2 hr under microwave irradiation. The mixture was poured into water at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (311 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (3H, d, J = 6.0 Hz), 1.59-1.80 (4H, m), 1.88-1.98 (4H, m), 3.89 (4H, s), 4.06-4.15 (1H, m), 4.72-4.99 (4H, m), 5.29-5.39 (1H, m), 7.40 (1H, d, J = 8.0 Hz),

7.47 (1H, s), 7.75 (1H, d, J = 8.0 Hz), 7.81 (1H, s), 8.81 (2H, s), 8.92 (1H, s), 9.35 (1H, s); MS *m/z* 627.4 $[M+1]^+$.

[0099]

C) 4-(2-{[1-(4-oxocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile

To a solution of 4-{2-[(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (311 mg) in MeOH (10 mL) was added 2 M aqueous hydrogen chloride solution (2.0 mL) at room temperature. The mixture was stirred at room temperature under normal pressure of nitrogen atmosphere overnight. The mixture was concentrated under reduced pressure. Saturated aqueous sodium hydrogencarbonate solution was added to the residue to adjust the pH to 7-8 and then the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (255 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (3H, d, J = 6.1 Hz), 2.11-2.41 (6H, m), 2.54-2.66 (2H, m), 4.47-4.60 (1H, m), 4.73-4.89 (3H, m), 4.91-4.99 (1H, m), 5.29-5.40 (1H, m), 7.40 (1H, d, J = 7.9 Hz), 7.47 (1H, s), 7.75 (1H, d, J = 8.1 Hz), 7.89 (1H, s), 8.80 (2H, s), 8.94 (1H, s), 9.35 (1H, s); MS *m/z* 583.4 $[M+1]^+$.

[0100]

D) 2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

To a mixture of 4-(2-{[1-(4-oxocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (100 mg), 2-oxa-6-azaspiro[3.3]heptane (84.6 mg) and AcOH (0.30 mL)

in MeOH (3.0 mL) was added 2-methylpyridine-borane (54.8 mg) at room temperature. The mixture was stirred at room temperature for 1 hr. The mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane and MeOH/ethyl acetate) to give the title compound (28.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ1.06-1.23 (2H, m), 1.53 (3H, d, J = 6.14 Hz), 1.60-1.82 (2H, m), 1.84-2.03 (3H, m), 2.08-2.22 (2H, m), 3.37 (4H, s), 3.80-3.95 (1H, m), 4.55-4.79 (7H, m), 4.82-5.03 (2H, m), 6.85 (1H, s), 6.95 (1H, s), 7.17 (1H, d, J = 7.98 Hz), 7.63 (1H, d, J = 8.07 Hz), 7.91 (1H, s), 8.55 (2H, s), 8.96 (1H, s).

[0101]

Example 7

(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

To a mixture of 4-{2-[(1-{2-azaspiro[3.3]heptan-6-yl}-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (100 mg), oxetan-3-one (61.5 mg) and AcOH (0.30 mL) in MeOH (3.0 mL) was added 2-methylpyridine-borane (36.5 mg) at room temperature. The mixture was stirred at room temperature for 14 hr. The mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/ethyl acetate) to give the title compound (30.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44-1.63 (3H, m), 2.60-2.71 (4H, m), 3.38 (4H, d, J = 14.10 Hz), 3.70-3.84 (1H, m), 4.39-4.56 (3H, m), 4.58-4.78 (5H, m), 4.80-5.03 (2H, m), 6.85 (1H, s), 6.89-7.00 (1H, m), 7.17 (1H, d, J = 7.98 Hz), 7.63 (1H, d, J = 7.89 Hz), 7.89 (1H, s), 8.56 (2H, s), 8.96 (1H, s).

[0102]

Example 8

4-(2-((1-((1r,4r)-4-(1-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)-2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)benzonitrile

A mixture of 4-(2-{[1-(4-oxocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (96.0 mg), bis(1-oxa-6-azaspiro[3.3]heptane) oxalate (71.2 mg) and 2-methylpyridine-borane (51.7 mg) in MeOH (3.3 mL) and AcOH (0.3 mL) was stirred at 60°C for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, MeOH/ethyl acetate/hexane) to give the title compound (40.3 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02-1.16 (2H, m), 1.35 (3H, d, J = 6.0 Hz), 1.59-1.72 (2H, m), 1.75-1.84 (2H, m), 1.90-2.02 (3H, m), 2.74 (2H, brt, J = 7.5 Hz), 2.98 (2H, d, J = 8.3 Hz), 3.47 (2H, d, J = 7.5 Hz), 3.87-3.98 (1H, m), 4.37 (2H, t, J = 7.6 Hz), 4.70-4.80 (2H, m), 4.80-4.89 (1H, m), 4.90-4.98 (1H, m), 5.30-5.39 (1H, m), 7.39 (1H, d, J = 8.2 Hz), 7.47 (1H, s), 7.75 (1H, d, J = 7.9 Hz), 7.78 (1H, s), 8.79 (2H, s), 8.89 (1H, s), 9.35 (1H, s).

[0103]

Example 9

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of 4-(2-{[1-(4-oxocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (96.0 mg), (1R,5S)-3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (73.9 mg), 2-methylpyridine-borane (51.7 mg) and triethylamine (165 mg) in MeOH (5.0 mL) and AcOH (0.50 mL) was stirred at 60°C for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (61.4 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09-1.21 (2H, m), 1.35 (3H, d, J = 5.9 Hz), 1.61-1.81 (6H, m), 2.02 (4H, dd, J = 12.7, 2.1 Hz), 2.08-2.19 (1H, m), 3.38-3.45 (2H, m), 3.48-3.56 (2H, m), 3.89-4.00 (1H, m), 4.76 (2H, q, J = 9.2 Hz), 4.81-4.90 (1H, m), 4.90-4.99 (1H, m), 5.29-5.40 (1H, m), 7.39 (1H, d, J = 7.9 Hz), 7.46 (1H, s), 7.75 (1H, d, J = 8.4 Hz), 7.79 (1H, s), 8.80 (2H, s), 8.90 (1H, s), 9.35 (1H, s), 2H were hidden by DMSO.

[0104]

Example 10

5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine

[0105]

A) 1-{1,4-dioxaspiro[4.5]decan-8-yl}-4-nitro-3-isopropyl-1H-pyrazole

A mixture of 4-nitro-3-isopropyl-1H-pyrazole (3.86 g), 1,4-dioxaspiro[4.5]decan-8-yl methanesulfonate (7.60 g) and cesium carbonate (16.1 g) in DMF (100 mL) was stirred at 120°C for 4 hr. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (5.21 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (6H, d, J = 6.9 Hz), 1.75 (2H, dd, J = 13.2, 4.1 Hz), 1.84-2.04 (4H, m), 2.15-2.25 (2H, m), 3.59 (1H, spt, J = 6.7 Hz), 3.98 (4H, s), 4.14-4.23 (1H, m), 8.15 (1H, s); MS *m/z* 296.2 $[M+1]^+$.

[0106]

B) 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-isopropyl-1H-pyrazol-4-amine

A mixture of 1-{1,4-dioxaspiro[4.5]decan-8-yl}-4-nitro-3-isopropyl-1H-pyrazole (5.20 g) and 10% palladium-carbon (1.70 g) in MeOH (60 mL) and THF (60 mL) was stirred at room temperature for 21 hr under normal pressure of hydrogen atmosphere. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give the title compound (4.13 g). This product was used in the next step without further purification.

MS *m/z* 266.2 $[M+1]^+$.

[0107]

C) 5-(4-chloro-3-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}phenyl)-N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine

A mixture of 2-chloro-5-(4-chloro-3-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)phenyl)pyrimidine (5.68 g), 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-isopropyl-1H-pyrazol-4-amine (4.13 g), $Pd_2(dba)_3$ (886 mg), BINAP (965 mg) and DBU (3.53 g) in DMA (50 mL) was stirred at 100°C for 3.5 hr. The reaction mixture was partitioned between ethyl acetate and water. The

organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane and MeOH/ethyl acetate) and silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (4.93 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (6H, d, J = 7.0 Hz), 1.44 (3H, d, J = 6.2 Hz), 1.71-1.81 (2H, m), 1.87-1.95 (2H, m), 1.99-2.04 (2H, m), 2.16-2.26 (2H, m), 2.95-3.00 (1H, m), 3.99 (4H, s), 4.17-4.28 (1H, m), 4.68-4.78 (1H, m), 4.82-4.92 (2H, m), 6.64 (1H, s), 6.89 (1H, s), 7.08 (1H, d, J = 8.4 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.94 (1H, s), 8.51 (2H, s), 8.97 (1H, s); MS *m/z* 580.4 $[M+1]^+$.

[0108]

D) 4-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-isopropyl-1H-pyrazol-1-yl)cyclohexan-1-one

2 M Aqueous hydrogen chloride solution (26 mL) was added to a solution of 5-(4-chloro-3-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}phenyl)-N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine (4.93 g) in MeOH (100 mL) at room temperature. The mixture was stirred at room temperature for 15.5 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane and MeOH/ethyl acetate), and the obtained solid was recrystallized from ethyl acetate/hexane to give the title compound (2.09 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.17 (6H, d, J = 6.9 Hz), 1.33 (3H, d, J = 6.1 Hz), 2.08-2.23 (2H, m), 2.25-2.40 (4H, m), 2.54-2.68 (2H, m), 3.07 (1H, dt, J = 13.9, 6.9 Hz), 4.54-4.67 (1H, m),

4.75-4.85 (1H, m), 4.86-4.95 (1H, m), 5.10-5.25 (1H, m), 7.25 (1H, d, J = 8.6 Hz), 7.37 (1H, s), 7.45 (1H, d, J = 8.3 Hz), 7.89 (1H, s), 8.71 (2H, s), 8.85 (1H, s), 9.37 (1H, s); MS *m/z* 536.4 $[M+1]^+$.

[0109]

E) 5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine

A mixture of 4-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-isopropyl-1H-pyrazol-1-yl)cyclohexan-1-one (150 mg), (1R,5S)-3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (125 mg), 2-methylpyridine-borane (88.0 mg) and triethylamine (282 mg) in MeOH (5.0 mL), THF (5.0 mL) and AcOH (0.50 mL) was stirred at 60°C for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (82.8 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12-1.28 (10H, m), 1.33 (3H, d, J = 6.1 Hz), 1.64-1.83 (6H, m), 1.98-2.08 (4H, m), 2.11-2.21 (1H, m), 3.00-3.10 (1H, m), 3.38-3.44 (2H, m), 3.49-3.56 (2H, m), 3.97-4.08 (1H, m), 4.76-4.85 (1H, m), 4.87-4.95 (1H, m), 5.13-5.23 (1H, m), 7.24 (1H, d, J = 8.3 Hz), 7.37 (1H, s), 7.45 (1H, d, J = 8.4 Hz), 7.80 (1H, s), 8.71 (2H, s), 8.82 (1H, s), 9.37 (1H, s).

[0110]

Example 11

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0111]

A) 4-nitro-1-(1,4-dioxaspiro[4.5]decan-8-yl)-3-(trifluoromethyl)-1H-pyrazole

The mixture of 4-nitro-3-(trifluoromethyl)-1H-pyrazole (3.55 g), 1,4-dioxaspiro[4.5]decan-8-yl methanesulfonate (4.63 g) and cesium carbonate (12.8 g) in DMF (50 mL) was stirred at 100°C for 15 hr. The mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.85 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.57-1.86 (4H, m), 2.00-2.13 (4H, m), 3.84-3.93 (4H, m), 4.39-4.58 (1H, m), 9.21 (1H, s); MS *m/z* 322.2 $[M+1]^+$.

[0112]

B) 4-[4-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl]cyclohexan-1-one

To a mixture of 4-nitro-1-(1,4-dioxaspiro[4.5]decan-8-yl)-3-(trifluoromethyl)-1H-pyrazole (4.67 g) and MeOH (100 mL) was added 2 M aqueous hydrogen chloride solution (20 mL). After being stirred at 60°C for 18 hr, the mixture was concentrated. The residue was dissolved in ethyl acetate, and the solution was washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.03 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 4.62-4.77 (m, 1H), 2.46-2.72 (m, 6H), 2.26-2.44 (m, 2H).

[0113]

C) 4-[(1r,4r)-4-[4-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl]cyclohexyl]morpholine

To a mixture of 4-[4-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl]cyclohexan-1-one (3.03 g), MeOH (80 mL) and AcOH

(8.0 mL) was added morpholine (2.00 g). After being stirred at room temperature for 10 min, 2-methylpyridine-borane (2.34 g) was added to the mixture. After being stirred at room temperature for 20 hr, the mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane and MeOH/ethyl acetate) to give the title compound (1.71 g).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36-1.42 (2H, m), 1.76-1.80 (2H, m), 1.82-1.83 (2H, m), 1.93-1.96 (2H, m), 2.12-2.15 (1H, m), 2.31-2.47 (4H, m), 3.57 (4H, t, J = 4.4 Hz), 4.31-4.38 (1H, m), 9.21 (1H, s); MS *m/z* 349.1 $[M+1]^+$.

[0114]

D) 1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-3-(trifluoromethyl)-1H-pyrazol-4-amine

A mixture of 4-[(1r,4r)-4-[4-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl]cyclohexyl]morpholine (15 g) and 10% palladium-carbon (1.2 g) in EtOH(200 mL) was stirred under normal pressure of hydrogen atmosphere at room temperature for 72 hr. The catalyst was removed by filtration, and then the filtrate was concentrated in vacuo to give the title compound (13.5 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25-1.45 (2H, m), 1.59-1.78 (2H, m), 1.86-1.94 (2H, m), 1.98-2.08 (2H, m), 2.19-2.33 (m, 1H), 2.48 (3H, d, J = 3.76 Hz), 3.56 (4H, brs), 3.90-4.08 (1H, m), 4.20 (2H, s), 7.22 (1H, s).

[0115]

E) 5-bromo-N-{1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-3-(trifluoromethyl)-1H-pyrazol-4-yl}pyrimidin-2-amine

To a mixture of 1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-3-(trifluoromethyl)-1H-pyrazol-4-amine (1.00 g) and 5-bromo-2-chloropyrimidine (1.82 g) in 1,3-dimethyl-2-imidazolidinone (10 mL) was added methanesulfonic acid (1.49 g) at room temperature. The mixture was stirred at 110°C under nitrogen

atmosphere for 14 hr. The mixture was diluted with ethyl acetate and extracted with 1 M aqueous hydrogen chloride solution. 8 M Aqueous sodium hydroxide solution was added to the aqueous layer to adjust the pH of the solution to 8-9, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/ethyl acetate) to give the title compound (430 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30-1.46 (2H, m), 1.68-1.83 (2H, m), 1.94 (2H, d, J = 11.3 Hz), 2.02-2.14 (2H, m), 2.27-2.37 (1H, m), 2.45-2.48 (4H, m), 3.53-3.60 (4H, m), 4.13-4.25 (1H, m), 8.08 (1H, s), 8.48 (2H, s), 9.01 (1H, s); MS *m/z* 476.2 $[M+1]^+$.

[0116]

F) 2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

To a mixture of 5-bromo-N-{1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-3-(trifluoromethyl)-1H-pyrazol-4-yl}pyrimidin-2-amine (430 mg), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)benzonitrile (353 mg) and cesium carbonate (586 mg) in THF (50 mL)/water (10 mL) was added bis(tri-tert-butylphosphine)palladium(0) (46.2 mg) at room temperature. The mixture was stirred at 70°C under nitrogen atmosphere for 10 hr, and quenched with water at room temperature. The insoluble material was removed by filtration, and the filtrate was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and silica gel column chromatography (MeOH/ ethyl acetate). The obtained solid was crystallized from ethyl acetate/hexane to give the title compound (230 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (3H, d, J = 6.2 Hz), 1.37-1.48 (2H, m), 1.70-1.86 (2H, m), 1.90-1.98 (2H, m), 2.06-2.15 (2H, m), 2.27-2.37 (1H, m), 2.51-2.56 (4H, m), 3.57 (4H, brs), 4.15-4.28 (1H, m), 4.79-4.88 (1H, m), 4.91-4.99 (1H, m), 5.29-5.39 (1H, m), 7.41 (1H, d, J = 7.5 Hz), 7.48 (1H, s), 7.76 (1H, d, J = 8.0 Hz), 8.14 (1H, s), 8.83 (2 H, s), 9.13 (1H, s), 9.34 (1H, s).

[0117]

Example 12

5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1r,4r)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine

A mixture of 4-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-isopropyl-1H-pyrazol-1-yl)cyclohexan-1-one (150 mg), 2-oxa-6-azaspiro[3.3]heptane (83.2 mg) and 2-methylpyridine-borane (88.0 mg) in MeOH (5.0 mL), THF (5.0 mL) and AcOH (0.50 mL) was stirred at 60°C for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, MeOH/ethyl acetate/hexane) to give the crude title compound (24.9 mg). This product was purified by preparative HPLC (water/CH_3CN containing 0.1% TFA). The desired fractions were concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated, washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (13.9 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96-1.11 (2H, m), 1.14 (6H, d, J = 7.0 Hz), 1.33 (3H, d, J = 6.0 Hz), 1.56-1.71 (1H, m), 1.71-1.71 (1H, m), 1.74-1.85 (2H, m), 1.90-2.07 (3H, m), 2.99-3.08 (1H,

m), 3.23 (4H, s), 3.91-4.04 (1H, m), 4.59 (4H, s), 4.76-4.84 (1H, m), 4.87-4.96 (1H, m), 5.13-5.23 (1H, m), 7.24 (1H, d, J = 8.0 Hz), 7.37 (1H, s), 7.44 (1H, d, J = 8.3 Hz), 7.79 (1H, s), 8.70 (2H, s), 8.80 (1H, s), 9.37 (1H, s).

[0118]

Example 13

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1S,4r)-4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (48.2 mg) and Amberlyst® A21 (300 mg) in MeOH (2.0 mL) was stirred at 5 min. The insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. To a mixture of the residue, 4-(2-{[1-(4-oxocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (104 mg) and AcOH (0.30 mL) in THF (3.0 mL) and MeOH (3.0 mL) was added 2-methylpyridine-borane (57.1 mg) at room temperature. The mixture was stirred at room temperature for 4 hr. The mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (41.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31-1.47 (2H, m), 1.53 (3H, d, J = 6.05 Hz), 1.73-1.92 (4H, m), 1.95-2.24 (4H, m), 2.40-2.56 (2H, m), 3.12 (1H, d, J = 10.00 Hz), 3.64 (1H, d, J = 7.80 Hz), 3.74 (1H, s), 3.84-3.99 (1H, m), 4.02-4.20 (1H, m), 4.41 (1H, s), 4.57-4.78 (3H, m), 4.81-5.02 (2H, m), 6.86 (1H, s), 6.96 (1H, s), 7.18 (1H, d, J = 7.98 Hz), 7.63 (1H, d, J = 8.16 Hz), 7.93 (1H, s), 8.56 (2H, s), 8.96 (1H, s).

[0119]

Example 14

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((2S,6R)-2,6-dimethylmorpholino)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

To a mixture of 4-(2-{[1-(4-oxocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (100 mg), (2R,6S)-2,6-dimethylmorpholine (39.3 mg) and AcOH (0.30 mL) in MeOH (3.0 mL) was added 2-methylpyridine-borane (54.8 mg) at room temperature. The mixture was stirred at room temperature for 4 hr. The mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and purified by preparative HPLC (water/CH_3CN containing 0.1% TFA). The desired fractions were neutralized with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (26.0 mg).

^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (6H, d, J = 6.14 Hz), 1.35-1.87 (7H, m), 1.90-2.15 (4H, m), 2.17-2.42 (3H, m), 2.73-2.88 (2H, m), 3.60-3.77 (2H, m), 3.80-3.96 (1H, m), 4.57-4.78 (3H, m), 4.81-5.03 (2H, m), 6.86 (1H, s), 6.95 (1H, s), 7.17 (1H, d, J = 8.10 Hz), 7.63 (1H, d, J = 7.98 Hz), 7.91 (1H, s) 8.56 (2H, s), 8.96 (1H, s).

[0120]

Example 15

(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile hydrochloride

[0121]

A) tert-butyl 4-(4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl)piperidine-1-carboxylate

To a solution of 4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazole (520 mg) in DMF (10 mL) was added 60% sodium hydride (118 mg) at 0°C. tert-Butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (895 mg) was added to the mixture at 0°C. The mixture was stirred at 70°C overnight. The mixture was quenched with water at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesuim sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (471 mg).

MS *m/z* 295.1 $[M+1-(Boc)]^+$.

[0122]

B) 4-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]piperidine

To a mixture of tert-butyl 4-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]piperidine-1-carboxylate (4.28 g) in toluene (4.0 mL) was added TFA (20 mL) at 5°C. The mixture was stirred at 5°C for 4 hr. The mixture was concentrated in vacuo, and the residue was poured into ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated and washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo to give the title compound (3.07 g).

MS *m/z* 295.3 $[M+1]^+$.

[0123]

C) 2-methyl-1-{4-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]piperidin-1-yl}propan-2-ol

A mixture of 4-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]piperidine (670 mg), 2,2-dimethyloxirane (1.62 g) and N,N-diisopropylethylamine (880 mg) in THF (0.5 mL) was

heated at 100°C for 3 hr under microwave irradiation. The mixture was poured into water and extracted twice with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (829 mg).

MS *m/z* 391.1 $[M+Na]^+$.

[0124]

D) 1-{4-[4-amino-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]piperidin-1-yl}-2-methylpropan-2-ol hydrochloride

A mixture of 2-methyl-1-{4-[4-nitro-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]piperidin-1-yl}propan-2-ol (680 mg) and 10% palladium-carbon (196 mg) in 5-10% hydrogen chloride-MeOH (1.47 g) and MeOH (20 mL) was stirred under normal pressure of hydrogen atmosphereat room temperature for 2 hr. The catalyst was removed by filtration, and then the filtrate was concentrated in vacuo to give the title comppound (530 mg). MS *m/z* 337.2 $[M+1]^+$.

[0125]

E) (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile hydrochloride

To a mixture of 1-{4-[4-amino-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]piperidin-1-yl}-2-methylpropan-2-ol hydrochloride (195 mg) in NMP (2 mL) was added (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (213 mg) at room temperature, and the mixture was stirred at 110°C for 3 hrs. The mixture was quenched with water and made basic with saturated aqueous sodium hydrogencarbonate solution. The mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel

column chromatography (NH, ethyl acetate/hexane) and silica gel column chromatography (MeOH/ethyl acetate). The fractions collected were further purified by preparative HPLC (water/CH_3CN containing 0.1% TFA) to give (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile (68.0 mg), which was treated 4 M hydrogen chloride-ethyl acetate (3.79 mg) as 1 eq of the product and crystallized from ethyl acetate to give the title compound (48.0 mg).

^1H NMR (300 MHz, DMSO-d_6) δ 1.28 (6H, brs), 1.36 (3H , d, J = 3.12 Hz), 2.19 (3H, brs), 2.41 (3H, brs), 3.13 (2H, brs), 3.65-3.84 (1H, m), 3.95-4.13 (1H, m), 4.23-4.47 (1H, m), 4.50-4.64 (2H, m), 4.71-4.92 (2H, m), 5.12-5.39 (2H, m), 7.43 (2H, brs), 7.68-7.80 (1H, m), 7.94 (2H, brs), 8.50 (1H, brs), 8.80 (2H, brs), 9.01 (1H, brs), 9.17-9.56 (1H, m).

[0126]

Example 16

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropyl-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0127]

A) tert-butyl N-[(1r,4r)-4-[4-nitro-3-(propan-2-yl)-1H-pyrazol-1-yl]cyclohexyl]carbamate

A mixture of 4-nitro-3-(propan-2-yl)-1H-pyrazole (4.00 g), tert-butyl N-[(1s,4s)-4-(methanesulfonyloxy)cyclohexyl]carbamate (15.0 g) and cesium carbonate (16.7 g) in DMA (75 mL) was stirred at 100°C for 9 hr. The reaction mixture was partitioned between ethyl acetate and 2 M aqueous hydrogen chloride solution. The organic layer was separated, washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and the obtained solid was recrystallized from ethyl acetate/hexane to give the title compound (640 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24-1.36 (8H, m), 1.45 (9H, s), 1.71-1.87 (2H, m), 2.16-2.30 (4H, m), 3.47-3.67 (2H, m), 4.00-4.11 (1H, m), 4.26-4.57 (1H, m), 8.11 (1H, s).

[0128]

B) (1r,4r)-4-[4-nitro-3-(propan-2-yl)-1H-pyrazol-1-yl]cyclohexan-1-amine hydrochloride

4 M Hydrogen chloride-ethyl acetate (0.91 mL) was added to a solution of tert-butyl N-[(1r,4r)-4-[4-nitro-3-(propan-2-yl)-1H-pyrazol-1-yl]cyclohexyl]carbamate (640 mg) in THF (20 mL) at room temperature. The mixture was stirred at room temperature for 20 hr. 4 M Hydrogen chloride-ethyl acetate (0.91 mL) was added at room temperature. The mixture was stirred at 60°C for 1.5 hr. The reaction mixture was concentrated under reduced pressure. The residue was treated with ethyl acetate and IPE to give the title compound. This product was used without further purification next step.
MS *m/z* 253.2 $[M+1]^+$.

[0129]

C) 4-[(1r,4r)-4-[4-nitro-3-(propan-2-yl)-1H-pyrazol-1-yl]cyclohexyl]morpholine

A mixture of (1r,4r)-4-[4-nitro-3-(propan-2-yl)-1H-pyrazol-1-yl]cyclohexan-1-amine hydrochloride (522 mg), potassium carbonate (1.00 g), 1-chloro-2-(2-chloroethoxy)ethane (258 mg) and sodium iodide (542 mg) in DMF (10 mL) was stirred at 100°C for 3 hr under argon atmosphere. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound. This product was diluted with ethyl acetate. The solution was washed with water (three times) and saturated brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (385 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (6H, d, J = 7.0 Hz), 1.40-1.51 (2H, m), 1.66-1.80 (2H, m), 2.08-2.18 (2H, m), 2.23-2.39 (3H, m), 2.59 (4H, d, J = 4.1 Hz), 3.59 (1H, dt, J = 13.7, 6.8 Hz), 3.74 (4H, d, J = 4.1 Hz), 3.98-4.09 (1H, m), 8.12 (1H, s); MS *m/z* 323.2 $[M+1]^+$.

[0130]

D) 3-(propan-2-yl)-1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-1H-pyrazol-4-amine dihydrochloride

A mixture of 4-[(1r,4r)-4-[4-nitro-3-(propan-2-yl)-1H-pyrazol-1-yl]cyclohexyl]morpholine (383 mg) and 10% palladium-carbon (113 mg) on carbon in 10% hydrogen chloride-MeOH (10 mL) was stirred at room temperature for 14 hr under normal pressure of hydrogen atmosphere. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give the title compound. This product was used without further purification next step.

MS *m/z* 293.3 $[M+1]^+$.

[0131]

E) 2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropyl-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (241 mg) and 3-(propan-2-yl)-1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-1H-pyrazol-4-amine dihydrochloride (215 mg) in NMP (1.0 mL) was stirred at 110°C for 22 hr under argon atmosphere. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/ethyl acetate) to give the desired product (175 mg). This product was purified by preparative HPLC (water/CH_3CN containing 0.1% TFA). The desired fractions were concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous

sodium hydrogencarbonate solution. The organic layer was separated, washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (113 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (6H, d, J = 6.8 Hz), 1.35 (3H, d, J = 5.9 Hz), 1.37-1.46 (2H, m), 1.63-1.77 (2H, m), 1.89-1.97 (2H, m), 2.04-2.13 (2H, m), 2.23-2.31 (1H, m), 3.00-3.10 (1H, m), 3.57 (4H, brs), 3.99-4.08 (1H, m), 4.80-4.89 (1H, m), 4.90-5.00 (1H, m), 5.29-5.42 (1H, m), 7.40 (1H, d, J = 8.3 Hz), 7.47 (1H, s), 7.75 (1H, d, J = 8.2 Hz), 7.81 (1H, s), 8.80 (2H, s), 8.98 (1H, s), 9.35 (1H, s), 4H were hidden by DMSO.

[0132]

Example 17

2-(((S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropyl-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of (S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (241 mg) and 3-(propan-2-yl)-1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-1H-pyrazol-4-amine dihydrochloride (215 mg) in NMP (1.0 mL) was stirred at 110°C for 22 hr under argon atmosphere. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/ethyl acetate) to give the crude desired product (144 mg). This crude was purified by preparative HPLC (water/CH_3CN containing 0.1% TFA). The desired fractions were concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated, washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (87.4 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (6H, d, J = 6.8 Hz), 1.35 (3H, d, J = 5.8 Hz), 1.37-1.49 (2H, m), 1.70 (2H, q, J = 12.3 Hz), 1.89-1.97 (2H, m), 2.04-2.14 (2H, m), 2.23-2.31 (1H, m), 3.00-3.10 (1H, m), 3.57 (4H, brs), 3.98-4.08 (1H, m), 4.56 (2H, d, J = 5.2 Hz), 5.19-5.32 (1H, m), 7.38 (1H, d, J = 7.8 Hz), 7.43 (1H, s), 7.73 (1H, d, J = 7.9 Hz), 7.81 (1H, s), 7.94 (1H, s), 8.49 (1H, s), 8.79 (2H, s), 8.97 (1H, s), 4H were hidden by DMSO.

[0133]

Example 18

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of 4-(2-{[1-(4-oxocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (200 mg), 8-oxa-3-azabicyclo[3.2.1]octane (220 mg) and 2-methylpyridine-borane (107 mg) in MeOH (5.0 mL) and AcOH (0.50 mL) was stirred at 60°C for 1.5 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, MeOH/ethyl acetate/hexane) to give the title compound (80.5 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.29-1.40 (5H, m), 1.62-1.74 (4H, m), 1.75-1.83 (2H, m), 1.89 (2H, d, J = 12.6 Hz), 2.05 (2H, d, J = 9.7 Hz), 2.15-2.25 (1H, m), 2.38 (2H, d, J = 10.5 Hz), 2.56 (2H, s), 3.85-3.98 (1H, m), 4.21 (2H, brs), 4.71-4.80 (2H, m), 4.81-4.89 (1H, m), 4.90-4.99 (1H, m), 5.30-5.40 (1H, m), 7.39 (1H, d, J = 8.3 Hz), 7.47 (1H, s), 7.75 (1H, d, J = 8.2 Hz), 7.78 (1H, s), 8.80 (2H, s), 8.89 (1H, s), 9.35 (1H, s).

[0134]

Example 19

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-(3-methoxy-3-methylazetidin-1-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

To a mixture of 4-(2-{[1-(4-oxocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (200 mg), 3-methoxy-3-methylazetidine hydrochloride (140 mg) and 2-methylpyridine-borane (107 mg) in MeOH (7.0 mL) and AcOH (0.70 mL) was added triethylamine (173 mg) at room temperature. The mixture was stirred at 60°C for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (100 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (3H, brs), 1.37-1.41 (3H, m), 1.61-1.74 (2H, m), 1.78-1.90 (2H, m), 1.97-2.06 (3H, m), 2.77-3.04 (2H, m), 3.10 (5H, s), 3.86-3.98 (1H, m), 4.71-4.80 (2H, m), 4.81-4.90 (1H, m), 4.90-4.99 (1H, m), 5.29-5.41 (1H, m), 7.39 (1H, d, J = 8.2 Hz), 7.47 (1H, s), 7.75 (1H, d, J = 8.3 Hz), 7.79 (1H, s), 8.80 (2H, s), 8.90 (1H, s), 9.35 (1H, s), 2H were not assigned.

[0135]

Example 20

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(1,1-difluoropropyl)-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0136]

A) N-methoxy-N-methyl-1-(oxan-2-yl)-1H-pyrazole-3-carboxamide

To a mixture of N-methoxy-N-methyl-1H-pyrazole-3-carboxamide (5.00 g) in THF (30 mL) were added 3,4-dihydro-2H-

pyran (7.6 mL) and 4-methylbenzene-1-sulfonic acid hydrate (791 mg) at room temperature. The mixture was stirred at 70°C under nitrogen atmosphere for 10 hr. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (880 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (2H, brs), 1.62-1.77 (1H, m), 1.94 (2H, d, J = 10.3 Hz), 2.03-2.17 (1H, m), 3.33 (3H, brs), 3.57-3.68 (1H, m), 3.70 (3H, s), 3.92 (1H, d, J = 11.2 Hz), 5.48 (1H, d, J=9.6 Hz), 6.67 (1H, s), 7.96 (1H, s); MS *m/z* 240.2 $[M+1]^+$.

[0137]

B) 1-[1-(oxan-2-yl)-1H-pyrazol-3-yl]propan-1-one

To a mixture of N-methoxy-N-methyl-1-(oxan-2-yl)-1H-pyrazole-3-carboxamide (880 mg) in THF (10 mL) was added bromo(ethyl)magnesium (11.0 mL) at 0°C. The mixture was stirred at room temperature under nitrogen atmosphere for 4 hr. The mixture was quenched with saturated aqueous ammonium chloride solution at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate /hexane) to give the title compound (690 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (3H, t, J = 7.3 Hz), 1.55 (2H, brs), 1.62-1.78 (1H, m), 1.94 (2H, d, J = 10.5 Hz), 2.04-2.18 (1H, m), 2.95 (2H, q, J = 7.4 Hz), 3.60-3.72 (1H, m), 3.94 (1H, d, J = 11.8 Hz), 5.51 (1H, d, J = 10.1 Hz), 6.74 (1H, s), 8.01 (1H, s); MS *m/z* 231.2 $[M+Na]^+$.

[0138]

C) 1-(1H-pyrazol-3-yl)propan-1-one

To a mixture of 1-[1-(oxan-2-yl)-1H-pyrazol-3-yl]propan-1-one (570 mg) in MeOH (10 mL) was added 2 M aqueous hydrogen

chloride solution (4.1 mL) at room temperature. The mixture was stirred at 50°C under nitrogen atmosphere for 10 hr. The mixture was concentrated in vacuo and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. This product (330 mg) was subjected to the next reaction without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (3H, t, J = 7.3 Hz), 2.97 (2H, q, J = 7.2 Hz), 6.70 (1H, brs), 7.86 (1H, s), 13.40 (1H, brs); MS *m/z* 125.2 $[M+1]^+$.

[0139]

D) 3-(1,1-difluoropropyl)-1H-pyrazole

To a mixture of 1-(1H-pyrazol-3-yl)propan-1-one (330 mg) in CH_3CN (20 mL) were added dropwise bis(2-methoxyethyl)(trifluoro-λ^4-sulfanyl)amine (1.45 mL) and EtOH (1 drop) at 0°C. The mixture was stirred at room temperature under nitrogen atmosphere for 14 hr. The mixture was quenched with saturated aqueous sodium hydrogencarbonate solution at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (327 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (3H, t, J = 7.4 Hz), 2.27 (2H, td, J = 16.2, 8.1 Hz), 6.45 (1H, brs), 7.81 (1H, brs), 13.15 (1H, brs); MS *m/z* 147.2 $[M+1]^+$.

[0140]

E) 3-(1,1-difluoropropyl)-4-nitro-1H-pyrazole

To a mixture of 3-(1,1-difluoropropyl)-1H-pyrazole (327 mg) in sulfuric acid (653 mg) was added dropwise nitric acid (275 µL) at 0°C. The mixture was stirred at 60°C-80°C for 14 hr. The mixture was quenched with iced water at 0°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium

sulfate and concentrated in vacuo. The insoluble material was removed by filtration, and the filtrate was concentrated in vacuo. This product (190 mg) was subjected to the next reaction without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.00 (2H, t, J = 7.4 Hz), 2.30-2.47 (2H, m), 8.83 (1H, brs), 8.99 (1H, brs).

[0141]

F) tert-butyl N-[(1r,4r)-4-[3-(1,1-difluoropropyl)-4-nitro-1H-pyrazol-1-yl]cyclohexyl]carbamate

To a solution of 3-(1,1-difluoropropyl)-4-nitro-1H-pyrazole (190 mg) and tert-butyl N-[(1s,4s)-4-[(4-methylbenzenesulfonyl)oxy]cyclohexyl]carbamate (1.10 g) in DMA (15 mL) was added cesium carbonate (970 mg) at room temperature. The mixture was stirred at 100°C under nitrogen atmosphere overnight. The mixture was quenched with water at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compoound (436 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.99 (3H, t, J = 7.7 Hz), 1.29-1.42 (11H, m), 1.74-1.92 (4H, m), 2.00-2.10 (2H, m), 2.25-2.44 (2H, m), 3.23-3.31 (1H, m), 4.15-4.30 (1H, m), 6.76-6.88 (1H, m), 8.25 (1H, s).

[0142]

G) (1r,4r)-4-[3-(1,1-difluoropropyl)-4-nitro-1H-pyrazol-1-yl]cyclohexan-1-amine hydrochloride

To a mixture of tert-butyl N-[(1r,4r)-4-[3-(1,1-difluoropropyl)-4-nitro-1H-pyrazol-1-yl]cyclohexyl]carbamate (436 mg) in EtOH (5.0 mL) was added 4 M hydrogen chloride-ethyl acetate (1.4 mL) at 0°C. The mixture was stirred at room temperature under nitrogen atmosphere for 4 hr. The mixture was concentrated in vacuo. This product was subjected to the next reaction without further purification.

MS *m/z* 289.2 $[M+1]^+$.

[0143]

H) 4-[(1r,4r)-4-[3-(1,1-difluoropropyl)-4-nitro-1H-pyrazol-1-yl]cyclohexyl]morpholine

To a mixture of (1r,4r)-4-[3-(1,1-difluoropropyl)-4-nitro-1H-pyrazol-1-yl]cyclohexan-1-amine hydrochloride (363 mg), potassium carbonate (155 mg) and 1-chloro-2-(2-chloroethoxy)ethane (158 mg) in DMA (5.0 mL) was added sodium iodide (499 mg) at room temperature. The mixture was stirred at 90°C under nitrogen atmosphere for 2 hr. The mixture was quenched with water at 60°C and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH /ethyl acetate) to give the title compound (122 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.99 (3H, t, J = 7.5 Hz), 1.28-1.46 (2H, m), 1.79 (2H, q, J = 12.4 Hz), 1.90-1.96 (2H, m), 2.05-2.16 (2H, m), 2.23-2.42 (3H, m), 2.45-2.49 (4H, m), 3.56 (4H, brs), 4.16-4.31 (1H, m), 8.25 (1H, s); MS *m/z* 359.3 $[M+1]^+$.

[0144]

I) 3-(1,1-difluoropropyl)-1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-1H-pyrazol-4-amine hydrochloride

A mixture of 4-[(1r,4r)-4-[3-(1,1-difluoropropyl)-4-nitro-1H-pyrazol-1-yl]cyclohexyl]morpholine (122 mg) and 10% palladium-carbon (196 mg) in ethyl acetate (3.0 mL)/EtOH (3.0 mL) was stirred under nitrogen atmosphere at room temperature for 10 hr. The catalyst was removed by filtration, and then the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give 3-(1,1-difluoropropyl)-1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-1H-pyrazol-4-amine (50.0 mg). To a solution of 3-(1,1-difluoropropyl)-1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-1H-pyrazol-4-amine (50.0 mg) in EtOH (1.0 mL) was added 4 M hydrogen chloride-ethyl acetate (1.0 mL). After

being stirred at room temperature for 30 min, the mixture was concentrated in vacuo. The residue was subjected to the next step without further purification.

MS *m/z* 329.3 $[M+1]^+$.

[0145]

J) 2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(1,1-difluoropropyl)-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of 3-(1,1-difluoropropyl)-1-[(1r,4r)-4-(morpholin-4-yl)cyclohexyl]-1H-pyrazol-4-amine hydrochloride (56.0 mg) and (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (94.3 mg) in NMP (3.0 mL) was stirred at 110°C under nitrogen atmosphere for 14 hr. 8 M Aqueous sodium hydroxide solution was added to the solution to adjust the pH of the solution to 9-10, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/ethyl acetate). The insoluble material (37.0 mg) in ethyl acetate/hexane (1:5) was collected by filtration, washed with ethyl acetate/hexane (1:5) and dried in vacuo to give the title compound (12.0 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (3H, t, J = 7.5 Hz), 1.32-1.45 (5H, m), 1.68-1.82 (2H, m), 1.92-2.01 (2H, m), 2.05-2.14 (2H, m), 2.23-2.34 (3H, m), 2.42-2.48 (4H, m), 3.57 (4H, brs), 4.07-4.23 (1H, m), 4.79-4.98 (2H, m), 5.29-5.41 (1H, m), 7.41 (1H, d, J = 8.3 Hz), 7.46-7.52 (1H, m), 7.76 (1H, d, J = 7.5 Hz), 8.08 (1H, s), 8.54 (1H, s), 8.83 (2H, s), 9.35 (1H, s).

[0146]

Example 21

(S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)pyrimidin-2-amine

[0147]

A) ethyl 1-acetyl-3-(propan-2-yloxy)-1H-pyrazole-4-carboxylate

Diisopropyl azodicarboxylate (4.48 g) was added to a suspension of ethyl 1-acetyl-3-hydroxy-1H-pyrazole-4-carboxylate (3.32 g), propan-2-ol (2.00 g) and triphenylphosphine (5.24 g) in toluene (50 mL) at room temperature. The mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.61 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, t, J = 7.1 Hz), 1.43 (6H, d, J = 6.1 Hz), 2.61 (3H, s), 4.29 (2H, q, J = 7.0 Hz), 5.05 (1H, dt, J = 12.3, 6.1 Hz), 8.52 (1H, s); MS *m/z* 199.1 [M+H-Ac]$^+$.

[0148]

B) ethyl 3-(propan-2-yloxy)-1H-pyrazole-4-carboxylate

Sodium ethoxide (803 mg) was added to a solution of ethyl 1-acetyl-3-(propan-2-yloxy)-1H-pyrazole-4-carboxylate (2.60 g) in EtOH (30 mL) at room temperature. The mixture was stirred at room temperature for 30 min. 1 M Aqueous hydrogen chloride solution (12 mL) was added thereto at 0°C. The resulting mixture was partitioned between ethyl acetate and saturated brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.05 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, t, J = 7.1 Hz), 1.41 (6H, d, J = 6.1 Hz), 4.27 (2H, q, J = 7.1 Hz), 4.93 (1H, spt, J = 6.3 Hz), 7.86 (1H, s), NH was not assigned; MS *m/z* 221.2 [M+Na]$^+$.

[0149]

C) tert-butyl 6-[4-(ethoxycarbonyl)-3-(propan-2-yloxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate

A mixture of ethyl 3-(propan-2-yloxy)-1H-pyrazole-4-carboxylate (1.02 g), tert-butyl 6-(methanesulfonyloxy)-2-

azaspiro[3.3]heptane-2-carboxylate (1.79 g) and cesium carbonate (3.32 g) in DMA (20 mL) was stirred at 100°C for 12 hr. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.94 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28-1.34 (3H, m), 1.39 (6H, d, J = 6.1 Hz), 1.44 (9H, s), 2.65 (2H, s), 2.67 (2H, s), 3.98 (4H, d, J = 3.9 Hz), 4.24 (2H, q, J = 6.7 Hz), 4.42 (1H, quin, J = 7.6 Hz), 4.94 (1H, dt, J = 12.3, 6.2 Hz), 7.65 (1H, s); MS *m/z* 394.3 $[M+1]^+$.

[0150]

D) 1-{2-[(tert-butoxy)carbonyl]-2-azaspiro[3.3]heptan-6-yl}-3-(propan-2-yloxy)-1H-pyrazole-4-carboxylic acid

2 M Aqueous sodium hydroxide solution (12 mL) was added to a solution of tert-butyl 6-[4-(ethoxycarbonyl)-3-(propan-2-yloxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate (1.93 g) in THF (15 mL) and MeOH (15 mL) at room temperature. The mixture was stirred at room temperature for 13 hr and at 50°C for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 1 M aqueous hydrogen chloride solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (1.76 g). This product was used without further purification next step.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42-1.44 (15H, m), 2.61-2.74 (4H, m), 3.99 (4H, d, J = 4.0 Hz), 4.46 (1H, quin, J = 7.6 Hz), 4.98-5.13 (1H, m), 7.75 (1H, s), CO_2H was not assigned; MS *m/z* 366.3 $[M+1]^+$.

[0151]

E) tert-butyl 6-(4-{[(benzyloxy)carbonyl]amino}-3-(propan-2-yloxy)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate

A mixture of 1-{2-[(tert-butoxy)carbonyl]-2-azaspiro[3.3]heptan-6-yl}-3-(propan-2-yloxy)-1H-pyrazole-4-carboxylic acid (1.75 g), diphenylphosphoryl azide (1.57 g), triethylamine (725 mg) and benzyl alcohol (2.58 g) in toluene (50 mL) was stirred at 100°C for 3.5 hr under argon atmosphere. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give a mixture of the title compound and tert-butyl 6-{4-[(benzyloxy)carbonyl]-3-(propan-2-yloxy)-1H-pyrazol-1-yl}-2-azaspiro[3.3]heptane-2-carboxylate. 2 M Aqueous sodium hydroxide solution (7.2 mL) was added to a solution of this mixture (2.35 g) in MeOH (25 mL) and THF (25 mL) at room temperature. The mixture was stirred at room temperature for 19 hr and at 50°C for 1.5 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 1 M aqueous hydrogen chloride solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane and MeOH/ethyl acetate) to give the title compound (1.15 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (6H, d, J = 6.1 Hz), 1.44 (9H, s), 2.60 (2H, brs), 2.62 (2H, brs), 3.94 (2H, s), 3.98 (2H, s), 4.33-4.43 (1H, m), 4.79-4.88 (1H, m), 5.17 (2H, s), 6.30 (1H, brs), 7.34-7.42 (5H, m), 7.57 (1H, s); MS *m/z* 471.3 $[M+1]^+$.

[0152]

F) tert-butyl 6-[4-amino-3-(propan-2-yloxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate

A mixture of tert-butyl 6-(4-{[(benzyloxy)carbonyl]amino}-3-(propan-2-yloxy)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (1.14 g) and 10% palladium-carbon (232 mg) in MeOH (12 mL) and THF (12 mL) was

stirred at room temperature for 4 hr under normal pressure of hydrogen atmosphere. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give the title compound. This product was used without further purification next step.

MS *m/z* 337.3 $[M+1]^+$.

[0153]

G) tert-butyl 6-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(propan-2-yloxy)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate

A mixture of 2-chloro-5-(4-chloro-3-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)phenyl)pyrimidine (467 mg), tert-butyl 6-[4-amino-3-(propan-2-yloxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate (407 mg), $Pd_2(dba)_3$ (55.4 mg), BINAP (75.3 mg) and DBU (275 mg) in DMA (12 mL) was stirred at 100°C for 1 hr under argon atmosphere. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane and MeOH/ethyl acetate) to give the title compound (186 mg).

^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (6H, d, J = 6.1 Hz), 1.42-1.46 (12H, m), 2.65 (2H, s), 2.68 (2H, s), 3.98 (2H, s), 4.00 (2H, s), 4.39-4.49 (1H, m), 4.67-4.75 (1H, m), 4.82-4.94 (3H, m), 6.86 (2H, d, J = 6.1 Hz), 7.07 (1H, d, J = 8.1 Hz), 7.44 (1H, d, J = 8.3 Hz), 7.86 (1H, s), 8.52 (2H, s), 8.96 (1H, s); MS *m/z* 651.3 $[M+1]^+$.

[0154]

H) N-(1-{2-azaspiro[3.3]heptan-6-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)-5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-amine

A mixture of tert-butyl 6-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-

yl]amino}-3-(propan-2-yloxy)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (183 mg) and TFA (1.59 g) was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure to give the title compound. This product was used without further purification next step.

MS *m/z* 551.3 $[M+1]^+$.

[0155]

I) (S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)pyrimidin-2-amine

A mixture of N-(1-{2-azaspiro[3.3]heptan-6-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)-5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-amine (77.1 mg), dihydro-2H-pyran-4(3H)-one (70.0 mg), 2-methylpyridine-borane (44.0 mg) and triethylamine (70.8 mg) in MeOH (7.0 mL) and AcOH (0.70 mL) was stirred at 60°C for 1 hr under argon atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane and MeOH/ethyl acetate) and preparative HPLC (water/CH_3CN containing 0.1% TFA). The desired fractions were concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated, washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (22.2 mg).

^1H NMR (300 MHz, DMSO-d_6) δ 1.06-1.17 (2H, m), 1.26 (6H, d, J = 6.1 Hz), 1.33 (3H, d, J = 6.1 Hz), 1.52-1.60 (2H, m), 2.07-2.16 (1H, m), 2.47 (4H, br s), 3.08 (2H, s), 3.16 (2H, s), 3.21-3.29 (2H, m), 3.75-3.83 (2H, m), 4.52 (1H, quin, J = 8.0 Hz), 4.69-

4.76 (1H, m), 4.77-4.85 (1H, m), 4.86-4.95 (1H, m), 5.17 (1H, td, J = 6.4, 3.8 Hz), 7.24 (1H, dd, J = 8.3, 1.9 Hz), 7.36 (1H, d, J = 1.9 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.74 (1H, s), 8.47 (1H, s), 8.70 (2H, s), 9.37 (1H, s).

[0156]

Example 22

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0157]

A) ethyl 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazole-4-carboxylate

A mixture of ethyl 3-(propan-2-yloxy)-1H-pyrazole-4-carboxylate (1.02 g), 1,4-dioxaspiro[4.5]decan-8-yl methanesulfonate (2.41 g) and cesium carbonate (3.32 g) in DMA (20 mL) was stirred at 100°C for 12 hr. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.40 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, t, J = 7.2 Hz), 1.38 (6H, d, J = 6.1 Hz), 1.64-1.76 (2H, m), 1.84-1.93 (2H, m), 2.00 (2H, d, J = 12.3 Hz), 2.09-2.20 (2H, m), 3.97 (5H, s), 4.24 (2H, q, J = 7.1 Hz), 4.85-5.00 (1H, m), 7.72 (1H, s); MS *m/z* 339.2 $[M+1]^+$.

[0158]

B) 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazole-4-carboxylic acid

2 M Aqueous sodium hydroxide solution (10.2 mL) was added to a solution of ethyl 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazole-4-carboxylate (1.39 g) in THF (15 mL) and MeOH (15 mL) at room temperature. The mixture was stirred at room temperature for 15 hr. 2 M Aqueous sodium hydroxide solution (4.0 mL) was added thereto, and the mixture

was stirred at 50°C for 2.5 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 1 M aqueous hydrogen chloride solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (1.17 g). This product was used without further purification next step.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (6H, d, J = 6.1 Hz), 1.65-1.77 (2H, m), 1.84-1.93 (2H, m), 1.94-2.07 (2H, m), 2.09-2.19 (2H, m), 3.98 (5H, s), 5.04 (1H, spt, J = 6.2 Hz), 7.82 (1H, s), CO_2H was not assigned; MS *m/z* 311.3 $[M+1]^+$.

[0159]

C) benzyl N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)carbamate

A mixture of 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazole-4-carboxylic acid (1.16 g), {[azido(phenoxy)phosphoryl]oxy}benzene (1.23 g), triethylamine (565 mg) and benzyl alcohol (2.01 g) in toluene (40 mL) was stirred at 100°C for 3.5 hr under argon atmosphere. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give a mixture of the title compound and benzyl 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazole-4-carboxylate. 2 M Aqueous sodium hydroxide solution (5.5 mL) was added to a solution of this mixture in MeOH (15 mL) and THF (15 mL) at room temperature. The mixture was stirred at room temperature for 19 hr and at 50°C for 1.5 hr. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 1 M aqueous hydrogen chloride solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified

by silica gel column chromatography (MeOH/ethyl acetate/hexane) to give the title compound (375 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (6H, d, J = 6.1 Hz), 1.59-1.65 (2H, m), 1.70 (2H, dd, J = 12.8, 4.3 Hz), 1.82-1.89 (2H, m), 1.99 (2H, d, J = 11.8 Hz), 3.96 (5H, s), 4.81 (1H, quin, J = 6.0 Hz), 5.17 (2H, s), 6.30 (1H, brs), 7.33-7.43 (5H, m), 7.62 (1H, s); MS *m/z* 416.3 $[M+1]^+$.

[0160]

D) 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-amine

8 M Aqueous sodium hydroxide solution (0.34 mL) was added to a solution of benzyl N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)carbamate (372 mg) in EtOH (5.0 mL) at room temperature. The mixture was stirred at 90°C for 22 hr. Ethyl acetate, citric acid and water were added to the reaction mixture to adjust the pH of the solution to 4. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (252 mg).

MS *m/z* 282.2 $[M+1]^+$.

[0161]

E) 4-{2-[(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile

A mixture of (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (305 mg), 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-amine (251 mg), $Pd_2(dba)_3$ (40.9 mg), BINAP (55.7 mg) and DBU (204 mg) in DMA (3.0 mL) was stirred at 100°C for 1 hr under argon atmosphere. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane and then MeOH/ethyl acetate) to give the title compound (121 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (6H, d, J = 6.2 Hz), 1.53 (3H, d, J = 6.1 Hz), 1.73 (2H, td, J = 13.2, 3.9 Hz), 1.85-1.95 (2H, m), 1.99-2.17 (4H, m), 3.99 (4H, s), 4.01-4.09 (1H, m), 4.69-4.78 (1H, m), 4.84-5.00 (3H, m), 6.88 (1H, s), 6.96 (1H, s), 7.18 (1H, d, J = 8.3 Hz), 7.63 (1H, d, J = 8.1 Hz), 7.93 (1H, s), 8.55 (2H, s), 8.98 (1H, s); MS *m/z* 587.4 $[M+1]^+$.

[0162]

F) 4-(2-{[1-(4-oxocyclohexyl)-3-(propan-2-yloxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile

2 M Aqueous hydrogen chloride solution (1.00 mL) was added to a solution of 4-{2-[(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (118 mg) in THF (4.0 mL) at room temperature. The mixture was stirred at room temperature for 74 hr. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (68.0 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (6H, d, J = 6.1 Hz), 1.52 (3H, d, J was not calculated), 2.31-2.56 (6H, m), 2.57-2.66 (2H, m), 4.36-4.46 (1H, m), 4.68-4.76 (1H, m), 4.83-4.99 (3H, m), 6.85 (1H, d, J = 1.3 Hz), 6.98 (1H, s), 7.18 (1H, dd, J = 8.1, 1.4 Hz), 7.63 (1H, d, J = 8.1 Hz), 7.96 (1H, s), 8.55 (2H, s), 8.95 (1H, s); MS *m/z* 543.3 $[M+1]^+$.

[0163]

G) 2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of 4-(2-{[1-(4-oxocyclohexyl)-3-(propan-2-yloxy)-1H-pyrazol-4-yl]amino}pyrimidin-5-yl)-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (65.0 mg),

and morpholine (52.1 mg) in MeOH (2.0 mL) and AcOH (0.20 mL) was stirred at 60°C for 1 hr under argon atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, MeOH/ethyl acetate/hexane). The obtained solid was purified by recrystallization from ethyl acetate/hexane to give the title compound (18.6 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25 (6H, d, J = 6.1 Hz), 1.35 (3H, d, J = 6.1 Hz), 1.36-1.48 (2H, m), 1.61-1.75 (2H, m), 1.88-1.97 (2H, m), 2.05 (2H, d, J = 11.8 Hz), 2.22-2.32 (1H, m), 2.47 (4H, brs), 3.54-3.60 (4H, m), 3.83-3.95 (1H, m), 4.71 (1H, dt, J = 12.3, 6.0 Hz), 4.80-4.88 (1H, m), 4.90-4.98 (1H, m), 5.30-5.38 (1H, m), 7.40 (1H, d, J = 7.8 Hz), 7.47 (1H, s), 7.72-7.77 (2H, m), 8.63 (1H, s), 8.79 (2H, s), 9.35 (1H, s).

[0164]

Example 23

5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)pyrimidin-2-amine

[0165]

A) 5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)-N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)pyrimidin-2-amine

A mixture of 2-chloro-5-(4-chloro-3-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)phenyl)pyrimidine (303 mg), 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-amine (220 mg), $Pd_2(dba)_3$ (35.9 mg), BINAP (48.8 mg) and DBU (178 mg) in DMA (3.0 mL) was stirred at 100°C for 1 hr under argon. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (MeOH/ethyl acetate and ethyl acetate/hexane) to give the title compound (183 mg). This product was used without further purification next step.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (6H, d, J = 6.1 Hz), 1.44 (3H, d, J = 5.9 Hz), 1.68-1.80 (2H, m), 1.86-1.93 (2H, m), 2.02-2.15 (4H, m), 3.99 (5H, s), 4.68-4.76 (1H, m), 4.82-4.91 (3H, m), 6.87 (1H, s), 6.89 (1H, s), 7.08 (1H, d, J = 8.4 Hz), 7.44 (1H, d, J = 8.1 Hz), 7.93 (1H, s), 8.52 (2H, s), 8.97 (1H, s); MS *m/z* 596.3 $[M+1]^+$.

[0166]

B) 4-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(propan-2-yloxy)-1H-pyrazol-1-yl)cyclohexan-1-one

A mixture of 5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)-N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)pyrimidin-2-amine (180 mg) and 2 M aqueous hydrogen chloride solution (1.5 mL) in THF (6.0 mL) was stirred at room temperature for 20 hr. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (124 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (6H, d, J = 6.2 Hz), 1.44 (3H, d, J = 6.1 Hz), 2.30-2.55 (6H, m), 2.57-2.67 (2H, m), 4.36-4.45 (1H, m), 4.67-4.75 (1H, m), 4.82-4.93 (3H, m), 6.87 (1H, d, J = 2.0 Hz), 6.89 (1H, s), 7.08 (1H, dd, J = 8.3, 2.0 Hz), 7.44 (1H, d, J = 8.3 Hz), 7.96 (1H, s), 8.52 (2H, s), 8.95 (1H, s); MS *m/z* 552.3 $[M+1]^+$.

[0167]

C) 5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)pyrimidin-2-amine

A mixture of 4-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(propan-2-yloxy)-1H-pyrazol-1-yl)cyclohexan-1-one (121 mg), morpholine (94.9 mg) and 2-methylpyridine-borane (68.8 mg) in MeOH (4.0 mL) and AcOH (0.40 mL) was stirred at 60°C for 1 hr under argon atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (33.5 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25 (6H, d, J = 6.1 Hz), 1.33 (3H, d, J = 6.1 Hz), 1.34-1.46 (2H, m), 1.61-1.74 (2H, m), 1.92 (2H, d, J = 12.0 Hz), 2.02-2.10 (2H, m), 2.22-2.32 (1H, m), 2.47 (4H, brs), 3.54-3.59 (4H, m), 3.82-3.94 (1H, m), 4.71 (1H, quin, J = 6.1 Hz), 4.76-4.84 (1H, m), 4.87-4.94 (1H, m), 5.13-5.22 (1H, m), 7.24 (1H, dd, J = 8.3, 1.8 Hz), 7.36 (1H, d, J = 1.7 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.72 (1H, s), 8.44 (1H, s), 8.70 (2H, s), 9.37 (1H, s).

[0168]

Example 24

(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-(2-(3,3,3-trifluoropropyl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of 4-{2-[(1-{2-azaspiro[3.3]heptan-6-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (43.3 mg), 1,1,1-trifluoro-3-iodopropane (89.5 mg) and N,N-diisopropylethylamine (103 mg) in CH_3CN (2.0 mL) was stirred at 80°C for 14 hr under argon atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was washed with

saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) and preparative HPLC (water/CH_3CN containing 0.1% TFA). The desired fractions were concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated, washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (1.8 mg).

^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (6H, d, J = 6.1 Hz), 1.53 (3H, d, J = 6.2 Hz), 2.12-2.23 (2H, m), 2.64 (4H, d, J = 8.0 Hz), 2.66-2.73 (2H, m), 3.35 (4H, d, J = 10.5 Hz), 4.45 (1H, quin, J = 7.9 Hz), 4.68-4.76 (1H, m), 4.83-4.98 (3H, m), 6.85 (1H, d, J = 1.3 Hz), 6.96 (1H, s), 7.17 (1H, dd, J = 8.1, 1.5 Hz), 7.62 (1H, d, J = 8.1 Hz), 7.86 (1H, s), 8.55 (2H, s), 8.96 (1H, s).

[0169]

Example 25

(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

[0170]

A) tert-butyl 6-(4-{[5-(4-cyano-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(propan-2-yloxy)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate

A mixture of (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-chloropyrimidin-5-yl)benzonitrile (454 mg), tert-butyl 6-[4-amino-3-(propan-2-yloxy)-1H-pyrazol-1-yl]-2-azaspiro[3.3]heptane-2-carboxylate (407 mg), $Pd_2(dba)_3$ (55.4 mg), BINAP (75.3 mg) and DBU (275 mg) in DMA (6.0 mL) was stirred at 100°C for 1 hr under argon atmosphere. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (MeOH/ethyl acetate and ethyl acetate/hexane) to give the title compound (106 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (6H, d, J = 6.4 Hz), 1.45 (9H, s), 1.52 (3H, br s), 2.65 (2H, s), 2.68 (2H, s), 3.98 (2H, s), 4.00 (2H, s), 4.41-4.49 (1H, m), 4.68-4.77 (1H, m), 4.84 (1H, s), 4.89-4.97 (2H, m), 6.85 (1H, s), 6.94 (1H, s), 7.17 (1H, br d, J = 8.8 Hz), 7.62 (1H, d, J = 8.3 Hz), 7.86 (1H, s), 8.55 (2H, s), 8.96 (1H, s); MS *m/z* 642.4 $[M+1]^+$.

[0171]

B) 4-{2-[(1-{2-azaspiro[3.3]heptan-6-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile

A mixture of tert-butyl 6-(4-{[5-(4-cyano-3-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(propan-2-yloxy)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (103 mg) and TFA (1.82 g) was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure to give the title compound. This product was used without further purification next step.

MS *m/z* 542.3 $[M+1]^+$.

[0172]

C) (S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile

A mixture of 4-{2-[(1-{2-azaspiro[3.3]heptan-6-yl}-3-(propan-2-yloxy)-1H-pyrazol-4-yl)amino]pyrimidin-5-yl}-2-{[(2S)-1-(1H-1,2,3,4-tetrazol-1-yl)propan-2-yl]oxy}benzonitrile (43.3 mg), oxetan-3-one (28.8 mg), 2-methylpyridine-borane (25.0 mg) and triethylamine (40.4 mg) in MeOH (3.0 mL) and AcOH (0.30 mL) was stirred at 60°C for 1 hr under argon atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer

was washed with saturated brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/ethyl acetate and ethyl acetate/hexane) and preparative HPLC (water/CH_3CN containing 0.1% TFA). This product was repeatedly purified by silica gel column chromatography (ethyl acetate/hexane and then MeOH/ethyl acetate) to give the title compound (0.3 mg).
^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (6H, d, J = 6.2 Hz), 1.53 (3H, d, J = 6.1 Hz), 2.65 (4H, d, J = 8.1 Hz), 3.37 (4H, d, J = 12.2 Hz), 3.72-3.80 (1H, m), 4.44-4.55 (3H, m), 4.66-4.76 (3H, m), 4.83-4.97 (3H, m), 6.85 (1H, d, J = 1.3 Hz), 6.95 (1H, s), 7.17 (1H, dd, J = 8.1, 1.5 Hz), 7.62 (1H, d, J = 8.1 Hz), 7.87 (1H, s), 8.55 (2H, s), 8.96 (1H, s).

[0173]

Example 26

5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-(oxetan-3-yloxy)-1H-pyrazol-4-yl)pyrimidin-2-amine

[0174]

A) ethyl 1-acetyl-3-(oxetan-3-yloxy)-1H-pyrazole-4-carboxylate

To a mixture of ethyl 1-acetyl-3-hydroxy-1H-pyrazole-4-carboxylate (3.32 g), oxetan-3-ol (1.31 g), triphenylphosphine (5.26 g) and toluene (50 mL) was added diisopropyl azodicarboxylate (3.9 mL). After being stirred at 60°C for 1 hr, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (4.24 g).
MS *m/z* 255.1 $[M+1]^+$.

[0175]

B) ethyl 3-(oxetan-3-yloxy)-1H-pyrazole-4-carboxylate

To a mixture of ethyl 1-acetyl-3-(oxetan-3-yloxy)-1H-pyrazole-4-carboxylate (4.24 g) and MeOH (50 mL) was added potassium carbonate (4.56 g). After being stirred at room temperature for 30 min, the mixture was poured into water and

extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.35 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25 (3H, t, J = 7.1 Hz), 4.17 (2H, q, J = 7.1 Hz), 4.50-4.60 (2H, m), 4.77-4.92 (2H, m), 5.37 (1H, quin, J = 5.5 Hz), 8.12 (1H, s), 12.62 (1H, d, J = 1.3 Hz); MS *m/z* 213.1 $[M+1]^+$.

[0176]

C) ethyl 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(oxetan-3-yloxy)-1H-pyrazole-4-carboxylate

To a mixture of ethyl 3-(oxetan-3-yloxy)-1H-pyrazole-4-carboxylate (1.35 g) and DMF (20 mL) was added 60% sodium hydride (272 mg) at 0°C. After being stirred at 0°C for 10 min, 1,4-dioxaspiro[4.5]decan-8-yl methanesulfonate (1.81 g) was added to the mixture. After being stirred at 50°C for 14 hr, the mixture was poured into saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (720 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, t, J = 7.2 Hz), 1.63-1.77 (2H, m), 1.80-2.01 (4H, m), 2.02-2.15 (2H, m), 3.89-4.02 (5H, m), 4.27 (2H, q, J = 7.2 Hz), 4.77-4.85 (2H, m), 4.88-4.97 (2H, m), 5.45 (1H, quin, J = 5.9 Hz), 7.74 (1H, s); MS *m/z* 353.2 $[M+1]^+$.

[0177]

D) 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(oxetan-3-yloxy)-1H-pyrazole-4-carboxylic acid

To a of ethyl 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(oxetan-3-yloxy)-1H-pyrazole-4-carboxylate (719 mg) and EtOH (10 mL) was added 8 M aqueous sodium hydroxide solution (0.50 mL). After being stirred at 80°C for 2 hr, the mixture was

neutralized with 1 M aqueous hydrogen chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The product was subjected to the next step without further purification.

[0178]

E) benzyl N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(oxetan-3-yloxy)-1H-pyrazol-4-yl)carbamate

To a mixture of 1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(oxetan-3-yloxy)-1H-pyrazole-4-carboxylic acid (661 mg), triethylamine (0.45 mL), benzyl alcohol (0.32 mL) and toluene (10 mL) was added diphenylphosphoryl azide (0.65 mL). After being stirred at room temperature for 1 hr and then at 100°C for 2 hr, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (741 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.59-1.76 (4H, m), 1.78-1.95 (4H, m), 3.87 (4H, s), 3.92-4.07 (1H, m), 4.48-4.58 (2H, m), 4.74-4.84 (2H, m), 5.08 (2H, s), 5.22-5.34 (1H, m), 7.27-7.45 (5H, m), 7.61 (1H, s), 8.75 (1H, brs); MS *m/z* 430.2 $[M+1]^+$.

[0179]

F) 5-(4-chloro-3-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}phenyl)-N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(oxetan-3-yloxy)-1H-pyrazol-4-yl)pyrimidin-2-amine

To a mixture of benzyl N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(oxetan-3-yloxy)-1H-pyrazol-4-yl)carbamate (523 mg) and MeOH (10 mL) was added 10% palladium-carbon (141 mg). After being stirred under normal pressure of hydrogen atmosphere at room temperature for 1 hr, the insoluble material was removed by filtration, and the filtrate was concentrated in vacuo. To a mixture of the residue and DMA (10 mL) were added 2-chloro-5-(4-chloro-3-(((2S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)phenyl)pyrimidine (501 mg), BINAP (74 mg), $Pd_2(dba)_3$ (109 mg) and DBU (0.27 mL). After being stirred under nitrogen atmosphere at 100°C for 20 hr, the mixture was poured into

water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (267 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.33 (3H, d, J = 6.24 Hz), 1.57-1.82 (4H, m), 1.83-1.96 (4H, m), 3.84-3.93 (4H, m), 3.98-4.08 (1H, m), 4.51-4.59 (2H, m), 4.75-4.85 (3H, m), 4.86-4.96 (1H, m), 5.12-5.24 (1H, m), 5.28-5.39 (1H, m), 7.25 (1H, d, J = 8.25 Hz), 7.38 (s, 1H), 7.45 (1H, d, J = 8.34 Hz), 7.79 (1H, s), 8.68-8.77 (3H, m), 9.37 (1H, s); MS *m/z* 610.4 $[M+1]^+$.

[0180]

G) 4-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-(oxetan-3-yloxy)-1H-pyrazol-1-yl)cyclohexan-1-one

A mixture of 5-(4-chloro-3-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}phenyl)-N-(1-{1,4-dioxaspiro[4.5]decan-8-yl}-3-(oxetan-3-yloxy)-1H-pyrazol-4-yl)pyrimidin-2-amine (1.87 g), AcOH (15 mL) and water (3.0 mL) was stirred at 80°C for 4 hr. After being cooled, the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate, and the solution was neutralized with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the titled compound (631 mg).

MS *m/z* 566.4 $[M+1]^+$.

[0181]

H) 5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-(oxetan-3-yloxy)-1H-pyrazol-4-yl)pyrimidin-2-amine

To a mixture of 4-(4-{[5-(4-chloro-3-{[(2S)-1-(1H-tetrazol-1-yl)propan-2-yl]oxy}phenyl)pyrimidin-2-yl]amino}-3-

(oxetan-3-yloxy)-1H-pyrazol-1-yl)cyclohexan-1-one (121 mg), (1R,5S)-3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (61 mg), MeOH (5.0 mL) and AcOH (0.5 mL) was added 2-methylpyridine-borane (50 mg). After being stirred at 70°C for 3 hr, (1R,5S)-3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (61.0 mg) and sodium triacetoxyborohydride (90 mg) were added to the mixture at room temperature. After being stirred at 70°C for 1 hr, the mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/ethyl acetate), silica gel column chromatography (NH, ethyl acetate/hexane) and preparative HPLC (water/CH_3CN containing 0.1% TFA). The desired fractions were concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the titled compound (10.0 mg).

^1H NMR (DMSO-d_6) δ 1.33 (3H, d, J = 6.1 Hz), 1.44-1.59 (2H, m), 1.69-1.81 (6H, m), 2.07-2.23 (2H, m), 2.29-2.37 (1H, m), 3.20-3.27 (2H, m), 3.27-3.31 (2H, m), 3.40-3.47 (2H, m), 3.49-3.59 (2H, m), 3.90-4.04 (1H, m), 4.53-4.61 (2H, m), 4.74-4.85 (3H, m), 4.86-4.95 (1H, m), 5.12-5.24 (1H, m), 5.28-5.38 (1H, m), 7.25 (1H, dd, J = 2.0, 8.3 Hz), 7.38 (1H, d, J = 1.8 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.76 (1H, s), 8.66-8.76 (3H, m), 9.37 (1H, s).

[0182]

The compounds of Examples 1 to 26 in the following tables were produced according to the methods described in the above-mentioned Examples, or methods analogous thereto. The compounds of Examples are shown in the following Table 1. MS in the table means actual measured value. The activity (IC_{50}) was calculated

in Experimental Example 1 and classified according to the following three activity ranks;

A: less than 10 nM,

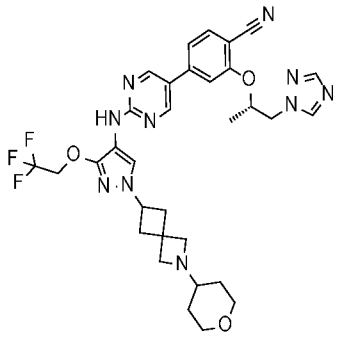
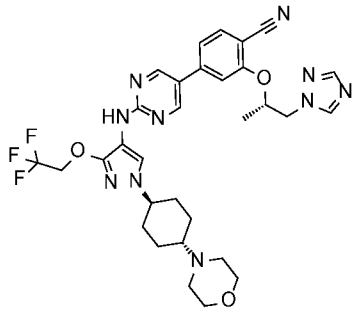
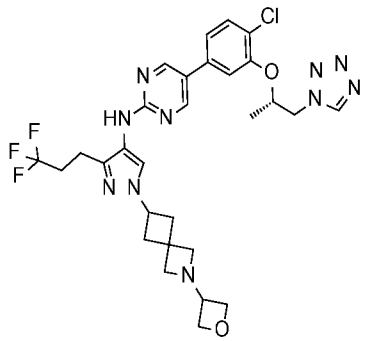
B: 10 nM or more and less than 100 nM,

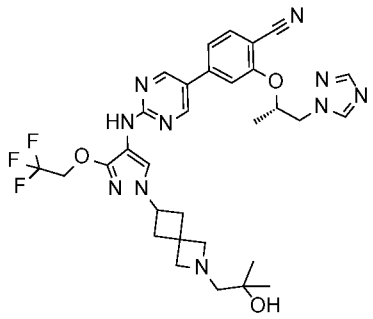
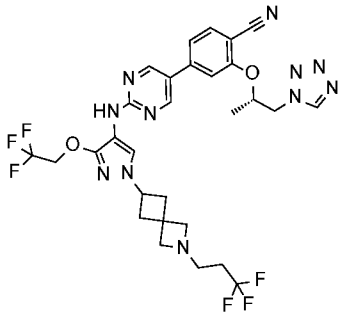
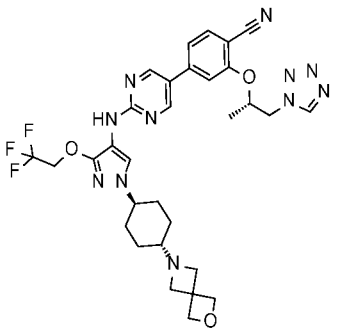
C: 100 nM or more.

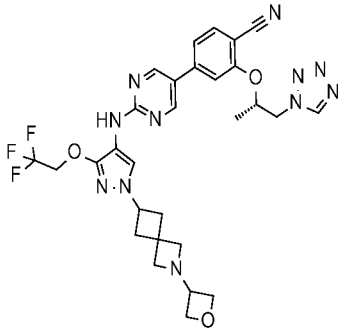
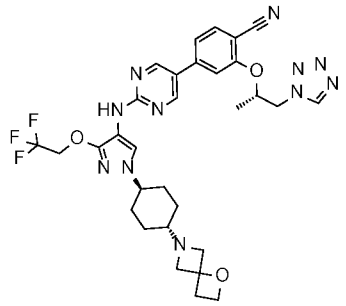
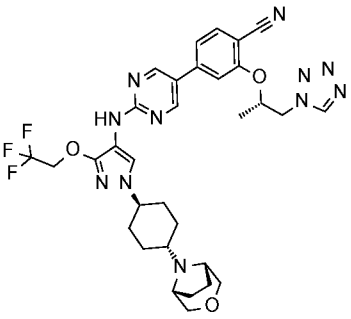
The activity of the compounds of Examples 1-24 and 26 was tested to be "A".

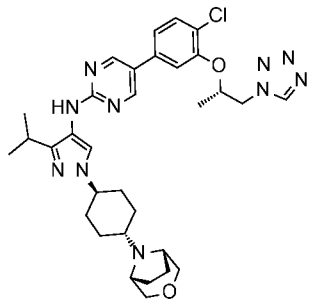
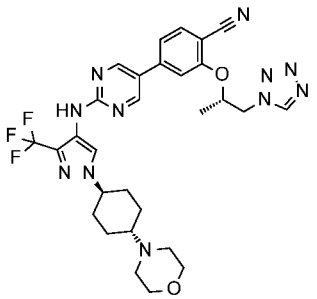
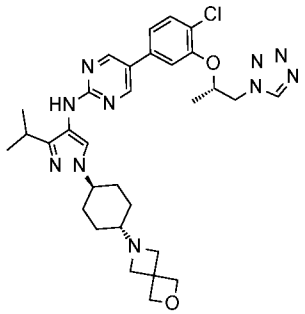
[0183]

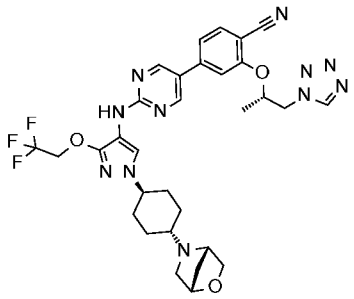
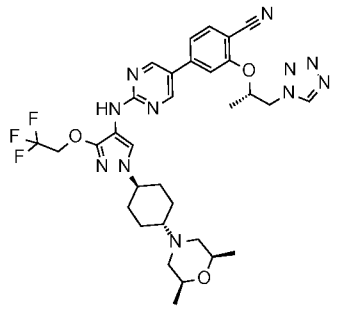
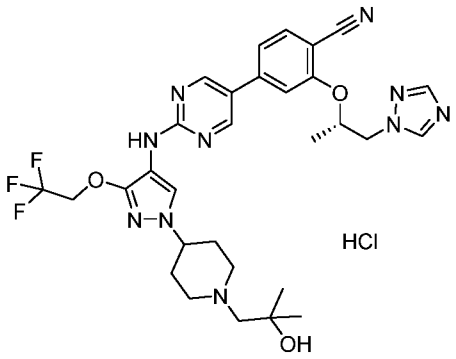
Table 1

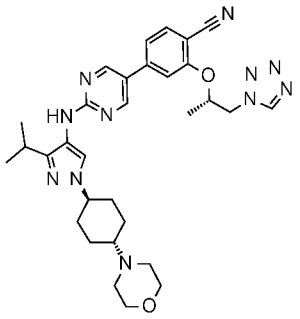
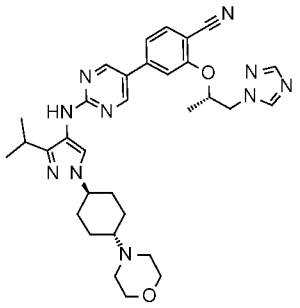
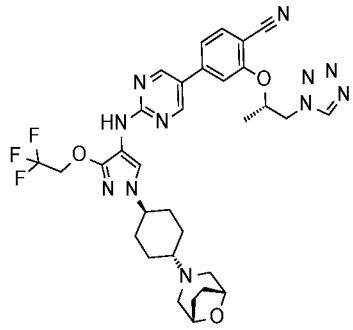
Ex. No.	IUPAC NAME	STRUCTURE	MS
1	(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		665.31
2	2-(((S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		653.30
3	(S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(3,3,3-trifluoropropyl)-1H-pyrazol-4-yl)pyrimidin-2-amine		645.33

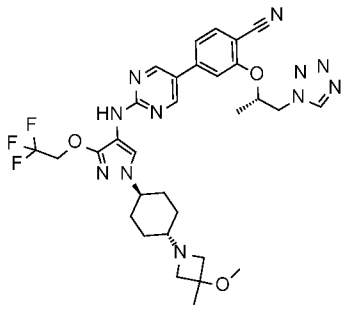
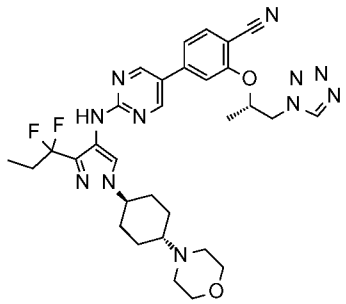
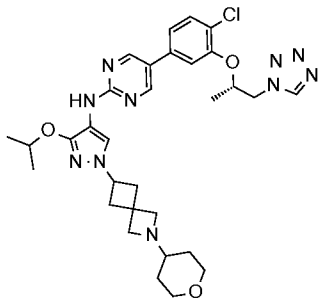
Ex. No.	IUPAC NAME	STRUCTURE	MS
4	(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(2-hydroxy-2-methylpropyl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		653.31
5	(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(2,2,2-trifluoroethoxy)-1-(2-(3,3,3-trifluoropropyl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		678.26
6	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		666.33

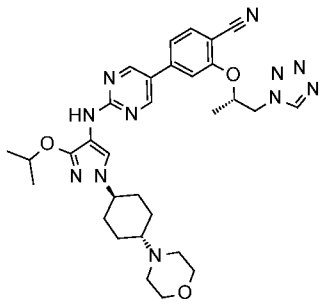
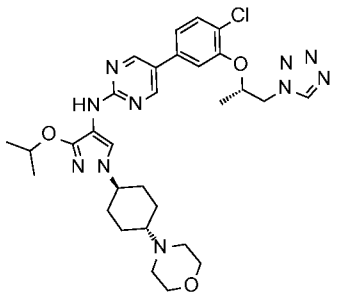
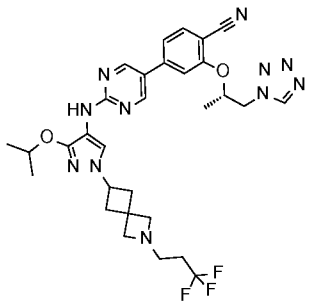
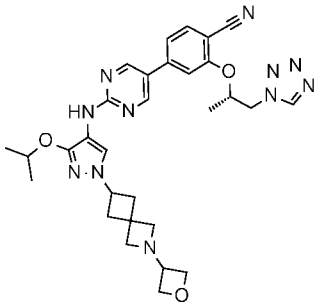
Ex. No.	IUPAC NAME	STRUCTURE	MS
7	(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		638.26
8	4-(2-((1-((1r,4r)-4-(1-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)-2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)benzonitrile		666.36
9	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		680.32

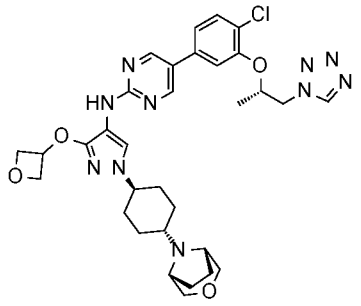
Ex. No.	IUPAC NAME	STRUCTURE	MS
10	5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine		633.38
11	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		624.31
12	5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1r,4r)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine		619.25

Ex. No.	IUPAC NAME	STRUCTURE	MS
13	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1S,4r)-4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		666.29
14	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((2S,6R)-2,6-dimethylmorpholino)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		682.34
15	(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile hydrochloride		641.34

Ex. No.	IUPAC NAME	STRUCTURE	MS
16	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropyl-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		598.32
17	2-(((S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropyl-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		597.38
18	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		680.30

Ex. No.	IUPAC NAME	STRUCTURE	MS
19	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-(3-methoxy-3-methylazetidin-1-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		668.29
20	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(1,1-difluoropropyl)-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		634.32
21	(S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)pyrimidin-2-amine		635.36

Ex. No.	IUPAC NAME	STRUCTURE	MS
22	2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		614.33
23	5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)pyrimidin-2-amine		623.30
24	(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-(2-(3,3,3-trifluoropropyl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		638.37
25	(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile		598.32

Ex. No.	IUPAC NAME	STRUCTURE	MS
26	5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-(oxetan-3-yloxy)-1H-pyrazol-4-yl)pyrimidin-2-amine		663.30

[0184]

Experimental Example 1

Evaluation of in vitro CaMKII inhibitory activity (binding assay)

[0185]

(i) Objective

In vitro CaMKIIδ inhibitory activity was evaluated by a binding assay.

[0186]

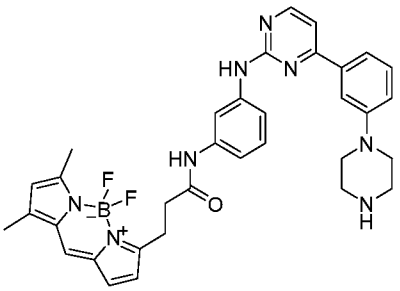
(ii) Materials

Full-length, glutathione-S-transferase(GST)-tagged, human CaMKIIδ was purchased from Carna Biosciences (product # 02-111, Kobe, Japan). Full-length bovine calmodulin was purchased from Wako Pure Chemical Industries (Osaka, Japan). Terbium-labeled anti-GST antibody (Tb-anti-GST Ab) was purchased from Life Technologies (Carlsbad, CA, USA). Boron-dipyrromethene (BODIPY)-labeled probe ligand was synthesized as described below.

[0187]

5,5-difluoro-7,9-dimethyl-3-(3-oxo-3-((3-((4-(3-(piperazin-1-yl)phenyl)pyrimidin-2-yl)amino)phenyl)amino)propyl)-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide

[0188]



[0189]

A) tert-butyl 4-(3-(2-chloropyrimidin-4-yl)phenyl)piperazine-1-carboxylate

A mixture of 2,4-dichloropyrimidine (500 mg, 3.36 mmol), tert-butyl 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate (1.24 g), tetrakis(triphenylphosphine)palladium(0) (739 mg), sodium carbonate (508 mg), THF (20 mL) and water (2.00 mL) was stirred at 60°C under nitrogen atmosphere for 24 hr. The mixture was quenched with water at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane) to give the title compound.

MS *m/z* 375.1 $[M+1]^+$.

[0190]

B) tert-butyl 4-(3-(2-((3-nitrophenyl)amino)pyrimidin-4-yl)phenyl)piperazine-1-carboxylate

A mixture of tert-butyl 4-(3-(2-chloropyrimidin-4-yl)phenyl)piperazine-1-carboxylate (704 mg), 3-nitroaniline (285 mg), palladium acetate (63.2 mg), BINAP (234 mg), cesium carbonate (857 mg) and toluene (10 mL) was stirred at 90°C under nitrogen atmosphere overnight. The mixture was quenched

with 1 M aqueous hydrogen chloride solution at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (NH, ethyl acetate/hexane) to give the title compound (588 mg).
MS *m/z* 477.2 $[M+1]^+$.

[0191]

C) tert-butyl 4-(3-(2-((3-aminophenyl)amino)pyrimidin-4-yl)phenyl)piperazine-1-carboxylate

A mixture of tert-butyl 4-(3-(2-((3-nitrophenyl)amino)pyrimidin-4-yl)phenyl)piperazine-1-carboxylate (588 mg) and 10% palladium-carbon (131 mg) in MeOH (15 mL) was stirred under normal pressure of hydrogen atmosphere at room temperature for 3 hr. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give the title compound (167 mg).
MS *m/z* 447.3 $[M+1]^+$.

[0192]

D) 3-(3-((3-((4-(3-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)pyrimidin-2-yl)amino)phenyl)amino)-3-oxopropyl)-5,5-difluoro-7,9-dimethyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide

1-Propanephosphonic acid cyclic anhydride (0.440 mL) was added to a solution of tert-butyl 4-(3-(2-((3-aminophenyl)amino)pyrimidin-4-yl)phenyl)piperazine-1-carboxylate (167 mg), 3-(2-carboxyethyl)-5,5-difluoro-7,9-dimethyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (109 mg), N,N-diisopropylethylamine (0.196 mL) and N,N-dimethylaminopyridine (45.7 mg) in ethyl acetate (4 mL) at room temperature. The mixture was stirred at 80°C under a dry atmosphere (calcium chloride tube) for 5 hr. The mixture was quenched with saturated aqueous sodium hydrogencarbonate solution at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with water and

saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane) to give the title compound (110 mg).

MS *m/z* 721.1 $[M+1]^+$.

[0193]

E) 5,5-difluoro-7,9-dimethyl-3-(3-oxo-3-((3-((4-(3-(piperazin-1-yl)phenyl)pyrimidin-2-yl)amino)phenyl)amino)propyl)-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide

4 M Hydrogen chloride-cyclopentyl methyl ether (0.382 mL) was added to a solution of 3-(3-((3-((4-(3-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)pyrimidin-2-yl)amino)phenyl)amino)-3-oxopropyl)-5,5-difluoro-7,9-dimethyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (110 mg) in ethyl acetate (2.00 mL) at room temperature. The mixture was stirred at room temperature under a dry atmosphere (calcium chloride tube) for 5 hr. After evaporation of the solvent, the residue was purified by preparative HPLC (water/CH_3CN containing 0.1% TFA). The desired fractions were neutralized with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulfate and concentrated in vacuo to give the title compound (15.0 mg). ^1H NMR (300 MHz, DMSO-d_6) δ 1.23 (3H, s), 2.27 (3H, s), 2.72-2.80 (3H, m), 2.82-2.94 (4H, m), 3.09-3.23 (6H, m), 6.31 (1H, s), 6.41 (1H, d, J = 3.9 Hz), 7.10 (2H, d, J = 3.9 Hz), 7.21 (2H, d, J = 7.7 Hz), 7.32-7.43 (2H, m), 7.49-7.56 (1H, m), 7.60 (1H, d, J = 8.3 Hz), 7.71 (2H, s), 8.05 (1H, s), 8.51 (1H, d, J = 5.0 Hz), 9.61 (1H, s), 9.99 (1H, s); MS *m/z* 621.2 $[M+1]^+$.

[0194]

(iii) Methods

Time-resolved fluorescence resonance energy transfer (TR-FRET) assay

All assays were conducted using 384-well, white, flat-bottomed plates (product # 784075, Greiner Bio-One,

Frickenhausen, Germany) in kinase assay buffer, which consists of 50 mM HEPES pH 7.6, 10 mM $MgCl_2$, 1 mM EGTA, 0.01% Brig-35, 0.1 mM DTT). The fluorescent probe ligand was added at a final concentration of 300 nM to solutions containing 0.21 nM Tb-anti-GST Ab, 1 mM $CaCl_2$, 10 µg/mL calmodulin, and 0.5 nM GST-tagged CaMKIIδ. After shaded incubation of the protein-probe mixture on ice for 30 min, the premix was dispensed in the assay plate including test inhibitors with 4 fold dilution series of eight concentrations. After 1 hr incubation at room temperature, TR-FRET signals were measured in duplicate using an EnVision microplate reader (Perkin Elmer, Waltham, MA, USA). The solution in each well was excited with a laser (λ = 340 nm) reflected by a dichroic mirror (D400/D505 (Perkin Elmer) through an excitation filter (UV (TRF) 340, (Perkin Elmer)), and fluorescence from Tb and BODIPY were detected through two emission filters (CFP 495 (Perkin Elmer) for Tb, Emission 520 (Perkin Elmer) for BODIPY).

The percentage of inhibition of test compounds was calculated according to equation (1)

$$\text{Inhibition } (\%) = 100 \times (\mu_H - T) / (\mu_H - \mu_L) \qquad (1)$$

Where T is the value of the wells containing test compounds and μ_H and μ_L are the mean values of the 0% and 100% inhibition control wells, respectively. The values of the 0 and 100% controls were the signals obtained in the absence and presence of 3 µM its parent compound, respectively. The half maximal inhibitory concentration (IC_{50}) of test compounds was calculated by fitting the data with the logistic equation using XLfit (IDBS, Guildford, UK). The IC_{50} was classified according to the following activity ranks.

A: less than 10 nM

B: 10 nM or more and less than 100 nM

C: 100 nM or more

[0195]

Experimental Example 2

Evaluation of *in vivo* cardiac CaMKII inhibition

[0196]

(i) Objective

To evaluate potency of test compounds to inhibit cardiac CaMKII kinase *in vivo*, phosphorylation levels of CaMKII-specific sites of phospholamban (Thr17, PLN) were measured in the heart of rats administered with test compounds at various doses.

[0197]

(ii) Materials and Methods

Test compounds were suspended in 0.5% [w/v] methylcellulose/water solution and administered 10 mg/kg) to male CD (SD) IGS rat (6-8 weeks old, n=4) by the p.o. route (5 mL/kg). At 4 hours after the administration, rats were sacrificed and the hearts were harvested. After washing the isolated hearts with ice-cold saline, connective tissues were removed on ice, and the isolated left ventricle were frozen into liquid nitrogen gas and stored at -80°C.

The left ventricle samples were homogenized in RIPA-buffer containing phosphatase inhibitors and protease inhibitors. Samples were analyzed by Western blotting using anti-P-PLN (Thr17, Santa Cruz Biotechnology, sc-17024-R) antibody. The band intensities were quantified using an imaging system and were normalized relative to the vehicle-treated group.

[0198]

(iii) Results

The results of the *in vivo* cardiac CaMKII inhibition are shown in Table 2.

[0199]

Table 2. Results of P-PLN reduction rate of each test compound in comparison with vehicle-treated group

Test compound (Example No.)	Dose	Time after administration	Reduction rate of P-PLN
2	10 mg/kg	4 hr	>50%
9	10 mg/kg	4 hr	>50%
13	10 mg/kg	4 hr	>50%
14	10 mg/kg	4 hr	>50%

[0200]

Formulation Examples

Medicaments containing the compound of the present invention as an active ingredient can be produced, for example, by the following formulations.

1. capsule

(1) compound obtained in Example 1		10 mg
(2) lactose		90 mg
(3) microcrystalline cellulose		70 mg
(4) magnesium stearate		10 mg
	1 capsule	180 mg

The total amount of the above-mentioned (1), (2) and (3) and 5 mg of (4) are blended and granulated, and 5 mg of the remaining (4) is added. The whole mixture is sealed in a gelatin capsule.

[0201]

2. tablet

(1) compound obtained in Example 1		10 mg
(2) lactose		35 mg
(3) cornstarch		150 mg
(4) microcrystalline cellulose		30 mg
(5) magnesium stearate		5 mg
	1 tablet	230 mg

The total amount of the above-mentioned (1), (2) and (3), 20 mg of (4) and 2.5 mg of (5) are blended and granulated, and 10 mg of the remaining (4) and 2.5 mg of the remaining (5) are added and the mixture is compression formed to give a tablet.

Industrial Applicability

[0202]

According to the present invention, a compound having a superior CaMKII inhibitory action, which is expected to be useful as an agent for the prophylaxis or treatment of cardiac diseases (particularly catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure, fatal arrhythmia) and the like can be provided.

CLAIMS

1. A compound selected from the group consisting of
(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
2-(((S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
(S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(3,3,3-trifluoropropyl)-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;
(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(2-hydroxy-2-methylpropyl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(2,2,2-trifluoroethoxy)-1-(2-(3,3,3-trifluoropropyl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
4-(2-((1-((1r,4r)-4-(1-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)-2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-morpholinocyclohexyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1r,4r)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)cyclohexyl)-3-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1S,4r)-4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((2S,6R)-2,6-dimethylmorpholino)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

(S)-2-((1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((1-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropyl-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-1,2,4-triazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropyl-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;

2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1R,4r)-4-((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)cyclohexyl)-3-

(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((1-((1r,4r)-4-(3-methoxy-3-methylazetidin-1-yl)cyclohexyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-(1,1-difluoropropyl)-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
(S)-5-(3-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-(2-(tetrahydro-2H-pyran-4-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;
2-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(3-isopropoxy-1-((1r,4r)-4-morpholinocyclohexyl)-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof;
(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-(2-(3,3,3-trifluoropropyl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof;
(S)-2-((1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-(2-((3-isopropoxy-1-(2-(oxetan-3-yl)-2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)amino)pyrimidin-5-yl)benzonitrile, or a salt thereof; and
5-(3-(((S)-1-(1H-tetrazol-1-yl)propan-2-yl)oxy)-4-chlorophenyl)-N-(1-((1R,4r)-4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)cyclohexyl)-3-(oxetan-3-yloxy)-1H-pyrazol-4-yl)pyrimidin-2-amine, or a salt thereof.

2. A medicament comprising the compound or salt according to claim 1.

3. The medicament according to claim 2, which is a calcium/calmodulin-dependent protein kinase II inhibitor.

4. The medicament according to claim 2, which is an agent for the prophylaxis or treatment of cardiac diseases.

5. The medicament according to claim 4, wherein the cardiac disease is selected from catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure and fatal arrhythmia.

6. The compound or salt according to claim 1 for use in the prophylaxis or treatment of cardiac diseases.

7. The compound or salt according to claim 6, wherein the cardiac disease is selected from catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure and fatal arrhythmia.

8. A method of inhibiting calcium/calmodulin-dependent protein kinase II in a mammal, which comprises administering an effective amount of the compound or salt according to claim 1 to the mammal.

9. A method for the prophylaxis or treatment of cardiac diseases in a mammal, which comprises administering an effective amount of the compound or salt according to claim 1 to the mammal.

10. The method according to claim 9, wherein the cardiac disease is selected from catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure and fatal arrhythmia.

11. Use of the compound or salt according to claim 1 for the production of an agent for the prophylaxis or treatment of cardiac diseases.

12. The use according to claim 11, wherein the cardiac disease is selected from catecholaminergic polymorphic ventricular tachycardia, postoperative atrial fibrillation, heart failure and fatal arrhythmia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/52722

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/506; C07D 239/28; A61P 9/06 (2019.01)

CPC - A61K 31/506; C07D 239/28; A61P 9/06

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0181991 A1 (ZHANG et al.) 16 July 2009 (16.07.2009) para [0029], pg 12, Table, compound 13	1-12
A	US 8,530,480 B2 (KAMENECKA et al.) 10 September 2013 (10.09.2013) col 29, ln 48-65, Example 1; col 234, ln 13-20	1-12
A	US 9,187,453 B2 (TAKEDA PHARMACEUTICAL COMPANY LIMITED) 17 November 2015 (17.11.2015) col 1, ln 5-12; col 93, 8-25; col 321, ln 28-40, Table 26	1-12
A	US 2017/0239264 A1 (PFIZER INC.) 24 August 2017 (24.08.2017) pg 65, Table, Ex 16	1-12
A	US 9,212,173 B2 (GENENTECH, INC.) 15 December 2015 (15.12.2015) col 37-38, Table 2; col 38, ln 40-44	1-12
X,P	WO 2018/183112 A1 (CARDURION PHARMACEUTICALS, LLC) 04 October 2018 (04.10.2018) Entire Document	1-12

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

* Special categories of cited documents:
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 November 2019	16 DEC 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300