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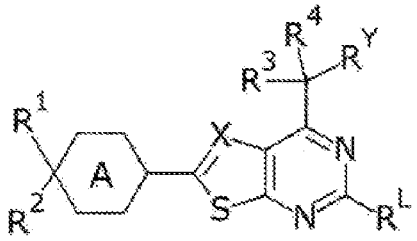
[続葉有]

(54) **Title**: SULFUR-CONTAINING BICYCLIC COMPOUND

(54) 発明の名称 : 含硫黄二環式化合物



(III)

(57) **Abstract**: [Problem] To provide a compound useful as a pharmaceutical composition for prevention and/or treatment of diseases such as schizophrenia. [Solution] The inventors developed the present invention upon investigating a pharmaceutical composition having effects as a GABAB positive allosteric modulator (effects as a PAM), for preventing/treating diseases such as schizophrenia, and confirming that a sulfur-containing bicyclic compound has effects as a GABAB PAM. This sulfur-containing bicyclic compound has effects as a GABAB PAM and can be used as a preventive and/or therapeutic agent for diseases such as schizophrenia. (In the formula, X represents CH, R^1 represents a lower alkyl, R^2 represents a lower alkyl , R^3 represents –H, R^4 represents –H, ring A is a cyclohexane ring, R^Y represents a group represented by formula (III), Y represents NH, etc., and R^L represents a lower alkyl.)

(57) 要約: 【課題】統合失調症等の予防及び/又は治療用医薬組成物として有用な化合物を提供する。 【解決手段】本発明者らは、GABAB のポジティブアロステリックモジュレート作用(PAM 作用)を有し、統合失調症等の予防及び/又は治療用医薬組成物について検討し、含硫黄二環式化合物が GABAB 受容体の PAM であることを確認し、本発明を完成した。本発明の含硫黄二環式化合物は GABAB の PAM 作用を有し、統合失調症等の予防及び／又は治療剤として使用し得る。 （式中、Ｘは、ＣＨ、R^1は、低級アルキル、R^2は、低級アルキル、R^3は、－Ｈ、R^4は、－Ｈ、Ａ環は、シクロヘキサン環、R^Yは、式（ＩＩＩ）で表される基 Ｙは、ＮＨ等、R^Lは、低級アルキルである。）

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DESCRIPTION

Title of Invention: SULFUR-CONTAINING BICYCLIC COMPOUND

Technical Field

[0001]

The present invention relates to a sulfur-containing bicyclic compound which is useful as an active ingredient for a pharmaceutical composition, in particular, a pharmaceutical composition for treating schizophrenia, cognitive impairment associated with schizophrenia (CIAS), cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, Charcot-Marie-Tooth disease, or the like.

Background Art

[0002]

γ-Aminobutyric acid (GABA) is a typical inhibitory neurotransmitter which activates both an ionotropic $GABA_A$ and a metabotropic $GABA_B$ receptor. The $GABA_B$ receptor is expressed in most of both presynaptic terminals and postsynaptic portions in the mammalian brain and adjusts the inhibitory synaptic transmission, and it thus has a wide range of physiological and psychopathological actions. The $GABA_B$ receptor is a G protein coupled receptor (GPCR), has a seven-transmembrane domain, and is structurally classified to a Class C. This Class C GPCRs have a particularly large extracellular region and functions by forming a homo- or hetero-dimer(s) (Neuropharmacology, 2011, Jan, vol. 60 (1), p. 82-92). The $GABA_B$ receptor forms a hetero-dimer of $GABA_{B1}$ and $GABA_{B2}$, and exerts a function as a receptor by the cooperation between the subunits. That is, only the $GABA_{B1}$ has a function for allowing a ligand of an orthosteric $GABA_B$ receptor to bind, and promotes the coupling and activating function of a G protein of $GABA_{B2}$. The activated $GABA_B$ receptor inhibits an adenylate cyclase and controls the openings of K^+ channels (GIRK) conjugated with G protein and voltage-dependent calcium channels.

[0003]

From the recent studies, there have been reports that mental disorders such as a cognitive impairment and the like are caused by dysfunction of GABA-mediated nerves in a patient (Trends in Neurosciences, 2012, vol. 35 (1), p. 57-67; Molecular Psychiatry, 2003, vol. 8 (8), p. 721-737, 715; Frontiers in Psychiatry, 2012, vol. 3, p. 51; and Neuroscience & Biobehavioral Reviews, 2012, Oct, vol. 36 (9), p. 2044-2055).

[0004]

Baclofen is a $GABA_B$ receptor-selective agonist and is clinically used. In preclinical trials, it has been reported that baclofen improves methanephetamine-induced

cognitive impairment in mice (European Journal of Pharmacology, 2009, vol. 602 (1), p. 101-104); methanephetamine- and MK-801-induced prepulse inhibition disorder (Neuropsychopharmacology, 2008, Dec, vol. 33 (13), p. 3164-3175); and social behavioral disorder, spatial memory disorder, and γ-band brain waves in genetically modified mice with NMDA receptor hypofunction (Translational Psychiatry, 2012, Jul 17, vol. 2, p. e142). It has been reported that R-baclofen is effective in a fragile X syndrome patient and an autism spectrum disorder (Science Translational Medicine, 2012, Sep 19, vol. 4 (152), p. 152ra127; and Journal of Autism and Development Disorders., 2014, Apr, vol. 44 (4), p. 958-964). It has also been reported that FMR1, a gene causing a fragile X syndrome, has a significant effect on the expression of numerous genes associated in an autism spectrum disorder (Nature, 2012, Dec, vol. 492, p. 382-386; and Cell, 2011, Jul, vol. 146 (2), p. 247-261).

[0005]

Baclofen has been clinically used for the treatment of spasticity, contracture, or rigidity, which is caused from spinocerebellar degeneration, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, stroke, head trauma, or the like (Neurology, 2004, Oct 26, vol. 63 (8), p. 1357-1363). It has also been reported that baclofen is effective in anxiety disorder (Journal of Pharmacology and Experimental Therapeutics, 2004, vol. 310, P. 952-963); substance addiction, for example, addiction to drugs such as nicotine, cocaine, morphine, and the like, or alcoholism (Advances in Pharmacology, 2010, vol. 58, p. 373-396; Drug and Alcohol Dependence, 2002, Feb1, vol. 65 (3), p. 209-220; and Synapse, 2003, Oct, vol. 50 (1), p. 1-6); pain, for example, neuropathic pain (European Journal of Pain, 2004, Aug, vol. 8(4), p. 377-383); and reflux esophagitis (Neurogastroenterology and Motility, 2012, Jun, vol. 24 (6), p. 553-559, e253).

[0006]

There is a report that γ-hydroxybutyric acid (GHB), a $GABA_B$ agonist, also improves the fatigue in fibromyalgia patients and is thus effective for fibromyalgia (Pain, 2011, vol. 152, p. 1007-1017). The symptom of fibromyalgia is similar to that of a chronic fatigue syndrome. The $GABA_B$ agonist is expected to be effective for the chronic fatigue syndrome.

[0007]

It has been reported that when $GABA_B$ signals are activated, the overexpression of PMP22 genes causing Charcot-Marie-Tooth disease type 1A is inhibited (European Journal of Neuroscience, 2004, May, vol. 19(10), p. 2641-2649; and Nature Reviews Drug Discovery, 2012, vol. 11, p. 589).

[0008]

It has been reported that a $GABA_B$ receptor is also present in the peripheral organs, such as spleen, lung, liver, intestine, stomach, esophagus, bladder, and the like

(Neuroscience, 2000, vol. 100 (1), p. 155-170; and The Journal of Biological Chemistry, 2000, Oct 13, vol. 275 (41), p. 32174-32181). Therefore, the $GABA_B$ receptor ligand is expected to be applied in the treatment of diseases in the peripheral organs.

[0009]

Thus, it is believed that a compound activating a $GABA_B$ receptor is useful for the prevention or treatment of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, Charcot-Marie-Tooth disease, or the like.

[0010]

On the other hand, baclofen has a narrow therapeutic window due to adverse side effects such as sedation, muscle weakness, and the like, and thus, its use is limited. A decrease in motor coordination, a decrease in a body temperature, and the like are also the side effects in baclofen therapy.

[0011]

A plurality of reports on a positive allosteric modulator (PAM) exist (Molecular Pharmacology, 2001, vol. 60 (5), p. 963-971; Journal of Pharmacology and Experimental Therapeutics, 2004, Sep, vol. 310 (3), p. 952-963; and Psychopharmacology (Berl), 2011, May, vol. 215(1), p. 117-128). The PAM of the $GABA_B$ receptor binds to a receptor at a site different from a site for binding to an endogenous ligand, thereby improving the function of the receptor. The PAM of the $GABA_B$ receptor does not exhibit an agonistic activity alone, but increases the affinity to a receptor of an endogenous GABA, and thus, it has an action to increase the Potency and Efficacy of the $GABA_B$ receptor. It is believed that due to these properties, the PAM of the $GABA_B$ receptor does not exhibit the side effects of the $GABA_B$ agonist (for example, the side effects of baclofen as described above) and has useful therapeutic effects.

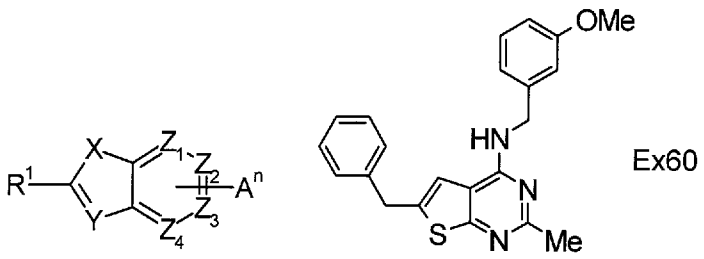
[0012]

Therefore, the PAM of the $GABA_B$ receptor has little side effects and is expected to be useful for the prevention or treatment of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, Charcot-Marie-Tooth disease, or the like.

[0013]

Patent Document 1 discloses a compound of the following general formula, which includes a compound represented by Ex60 as a drug for treating schizophrenia.

[Chem. 1]

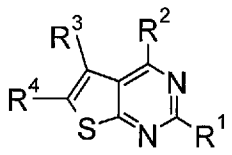


(In the formula, definition of R^1 includes many groups. As one of those groups, R^1 is a cycloalkyl group which may be substituted, or the like. Definition of A^n includes many groups. As one of those groups, A^n is an alkyl group which may be substituted, or the like. For the other symbols in the formula, refer to Patent Document 1.)

[0014]

Patent Document 2 discloses that an mGluR1 inhibitor represented by the following general formula is useful for Parkinson's disease, migraine, or the like.

[Chem. 2]

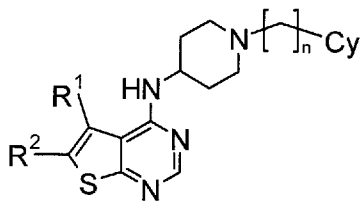


(In the formula, R^2 represents -N (R^{2a}) R^{2b}, -O-R^{2a}, or -S-R^{2a}. For the other symbols in the formula, refer to Patent Document 2.)

[0015]

Patent Document 3 discloses that a 5-HT antagonist represented by the following general formula is useful as a drug for treating for a neuropathological disease.

[Chem. 3]



(For the symbols in the formula, refer to Patent Document 3.)

Related Art

Patent Document

[0016]

[Patent Document 1] International Publication WO 2006/030031

[Patent Document 2] International Publication WO 02/062803
[Patent Document 3] International Publication WO 2004/089312

Disclosure of Invention

Problems to Be Solved by the Invention

[0017]

The present invention provides a sulfur-containing bicyclic compound which is useful as an active ingredient for a pharmaceutical composition, in particular, a pharmaceutical composition for treating schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, Charcot-Marie-Tooth disease, or the like.

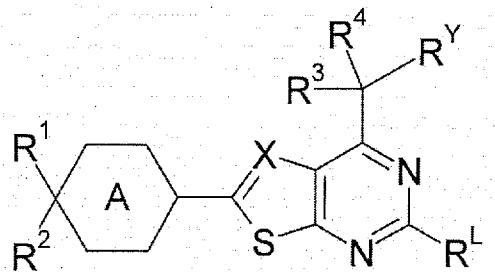
Means for Solving the Problems

[0018]

The present inventors have conducted extensive studies on PAM of a $GABA_B$ receptor, and as a result, they have found that a sulfur-containing bicyclic compound is the PANM of the $GABA_B$ receptor, thereby completing the present invention.

That is, the present invention relates to a compound of the formula (I) or a salt thereof, as well as a pharmaceutical composition comprising a compound of the formula (I) or a salt thereof and an excipient.

[Chem. 4]



(I)

(in the formula,

X is CH,

R^1 is lower alkyl,

R^2 is lower alkyl,

in which R^1 and R^2 may form a cycloalkane together with carbon atoms to which they are bonded,

R^3 is -H,

R^4 is -H,

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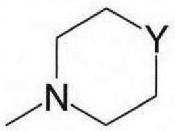
A ring is a cyclohexane ring,

R^Y is $-NR^AR^B$,

R^A and R^B form cyclic amino which may be substituted, together with a nitrogen atom to which they are bonded,

in which the cyclic amino is a group represented by the following formula (III):

[Chem. 5]



(III)

,

Y is NH, O, S, S $(=O)_2$, or CH_2, and

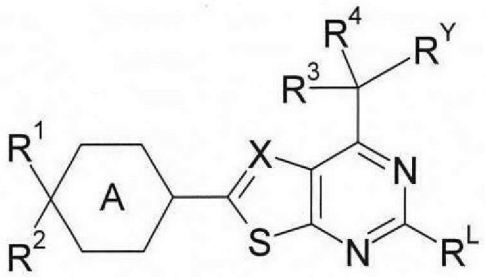
R^L is lower alkyl).

In addition, unless otherwise specified, when symbols in a certain chemical formula in the present specification are also used in another chemical formula, the same symbol represents the same meaning.

[0018a]

In a first aspect the present invention provides a compound of the formula (I) or a salt thereof:

[Chem. 20]



(I)

(in the formula,

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X is CH,

R^1 is lower alkyl,

R^2 is lower alkyl,

in which R^1 and R^2 may form a cycloalkane together with carbon atoms to which they are bonded,

R^3 is -H,

R^4 is -H,

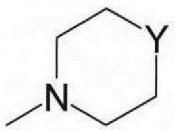
A ring is a cyclohexane ring,

R^Y is $-NR^AR^B$,

R^A and R^B form cyclic amino which may be substituted, together with a nitrogen atom to which they are bonded,

in which the cyclic amino is a group represented by the following formula (III):

[Chem. 21]



(III)

,

Y is NH, O, S, S $(=O)_2$, or CH_2, and

R^L is lower alkyl).

[0018b]

In a second aspect the present invention provides a pharmaceutical composition comprising the compound or salt thereof according to the first aspect and a pharmaceutically acceptable excipient.

[0018c]

In a third aspect the present invention provides use of the compound or salt thereof according to the first aspect for the preparation of a pharmaceutical composition for preventing or treating a disease selected from the group consisting of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, and Charcot-Marie-Tooth disease.

[0018d]

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In a fourth aspect the present invention provides use of the compound or salt thereof according to the first aspect for preventing or treating a disease selected from the group consisting of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, and Charcot-Marie-Tooth disease.

[0018e]

In a fifth aspect the present invention provides the compound or salt thereof according to the first aspect for preventing or treating a disease selected from the group consisting of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, and Charcot-Marie-Tooth disease.

[0018f]

In a sixth aspect the present invention provides a method for preventing or treating a disease selected from the group consisting of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, and Charcot-Marie-Tooth disease, comprising administering to a subject in need thereof an effective amount of the compound or salt thereof according to the first aspect.

[0019]

Further, the present invention relates to:

(1) a pharmaceutical composition for preventing or treating schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, or Charcot-Marie-Tooth disease, comprising a compound of the formula (I) or a salt thereof; where the pharmaceutical composition includes an agent for treating schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, or Charcot-Marie-Tooth disease, comprising a compound of the formula (I) or a salt thereof;

(2) use of a compound of the formula (I) or a salt thereof for the preparation of a pharmaceutical composition for preventing or treating schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, or Charcot-Marie-Tooth disease;

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(3) use of a compound of the formula (I) or a salt thereof for preventing or treating schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, or Charcot-Marie-Tooth disease;

(4) a compound of the formula (I) or a salt thereof for preventing or treating schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, or Charcot-Marie-Tooth disease;

(5) a method for preventing or treating schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, or Charcot-Marie-Tooth disease, comprising administering to a subject an effective amount of a compound of the formula (I) or a salt thereof.

Meanwhile, the term "subject" is a human being or another animal in need of prevention or treatment thereof, and according to a certain embodiment, a human being in need of prevention or treatment thereof.

Effects of the Invention

[0020]

The compound of the formula (I) or a salt thereof has a PAM action of a $GABA_B$ receptor, and can be used as an agent for preventing and/or treating schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, Charcot-Marie-Tooth disease, or the like.

Embodiments for Carrying Out the Invention

[0021]

Hereinafter, the present invention will be described in detail.

The "lower alkyl" is straight or branched chain alkyl having 1 to 6 carbon atoms (hereinafter simply referred to as C_{1-6}), for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, or the like, in another embodiment, C_{1-4} alkyl, and in a further embodiment, methyl.

[0022]

The "lower alkylene" is straight or branched C_{1-6} alkylene, for example, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, ethylethylene, 1,2-dimethylethylene, 1,1,2,2-tetramethylethylene, or the like, in another embodiment, C_{1-4} alkylene, and in a further embodiment, ethylene.

[0023]

The "halo-lower alkyl" is C_{1-6} alkyl substituted with one or more halogen atoms, in another embodiment, lower alkyl substituted with 1 to 5 halogen atoms, in a further embodiment, lower alkyl substituted with 1 to 3 halogen atoms, and in a still further embodiment, $-CF_3$.

[0024]

The "halogen" means F, Cl, Br, or I.

[0025]

The "cycloalkane" is a C_{3-8} saturated hydrocarbon ring, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, or cyclooctane, in

another embodiment, C_{5-6} cycloalkane, in a further embodiment, cyclohexane, and in a still further embodiment, cyclopropane.

[0026]

The "cycloalkyl" is a C_{3-8} saturated hydrocarbon ring group, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, in another embodiment, C_{5-6} cycloalkyl, in a further embodiment, cyclohexyl, and in a still further embodiment, cyclopropyl.

[0027]

In the present specification, the expression "which may be substituted" means "which is not substituted" or "which is substituted with 1 to 5 substituents", and in another embodiment, "which is not substituted" or "which is substituted with 1 to 3 substituents". Further, if it has a plurality of substituents, the substituents may be the same as or different from each other.

[0028]

In the present specification, with respect to the expression "R^A and R^B form cyclic amino which may be substituted, together with a nitrogen atom to which they are bonded", examples of the substituent which may be used for substitution in cyclic amino include the groups selected from the following Group Z.

Group Z:

(1) =O,

(2) -OH,

(3) -O-lower alkyl,

(4) halogen,

(5) -CN,

(6) lower alkyl,

(7) halo-lower alkyl,

(8) lower alkylene-OH,

(9) lower alkylene-O-lower alkyl,

(10) -C(=O)-lower alkyl,

(11) -C(=O)-lower alkylene-OH,

(12) -C(=O)-lower alkylene-CN, and

(13) cycloalkyl.

[0029]

In a certain aspect, examples of the "group selected from the Group Z" include the groups selected from the following Group Z1.

Group Z1:

(1) -OH,

(2) lower alkyl, and

(3) -C(=O)-lower alkylene-OH.

[0030]

Certain aspects of the present invention are shown below.

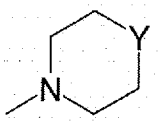
[1] A compound represented by the formula (I) or a salt thereof, in which

R^Y is $-NR^AR^B$,

R^A and R^B form cyclic amino which may be substituted with R^0, together with a nitrogen atom to which they are bonded,

in which the cyclic amino is a group represented by the following formula (III):

[Chem. 6]



(III)

, and

R^0 is a group selected from the following Group Z:

Group Z:

(1) =O,

(2) -OH,

(3) -O-lower alkyl,

(4) halogen,

(5) -CN,

(6) lower alkyl,

(7) halo-lower alkyl,

(8) lower alkylene-OH,

(9) lower alkylene-O-lower alkyl,

(10) -C(=O)-lower alkyl,

(11) -C(=O)-lower alkylene-OH,

(12) -C(=O)-lower alkylene-CN, and

(13) cycloalkyl.

[2] The compound or a salt thereof as described in [1], in which the group selected from the Group Z is a group selected from:

Group Z1:

(1) -OH,

(2) lower alkyl, and

(3) -C(=O)-lower alkylene-OH.

[3] The compound of the formula (I) or a salt thereof, in which Y is O, S, or $S(=O)_2$.

[4] The compound of the formula (I) or a salt thereof, in which R^L is CH_3.

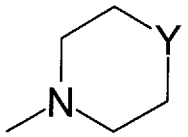
[5] The compound or a salt thereof, which is a combination of two or more groups of the groups described in the embodiments [1] to [4].

[0031]

Examples of the combination of the present invention are shown below.

[6] The compound of the formula (I) or a salt thereof, in which X is CH, Ring A is a cyclohexane ring, R^1 is lower alkyl, R^2 is lower alkyl, R^3 is -H, R^4 is -H, R^Y is represented by the following formula (III) which may be substituted:

[Chem. 7]



(III)

,

Y is O, S, or $S(=O)_2$, and R^L is lower alkyl.

[0032]

Examples of the specific compounds included in the present invention include the following compounds or salts thereof:

6-(4,4-dimethylcyclohexyl)-4-[(1,1-dioxo-1λ^6-thiomorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine,

trans-1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidine-3,4-diol,

1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidin-4-ol,

6-(4,4-dimethylcyclohexyl)-2-methyl-4-(thiomorpholin-4-ylmethyl)thieno[2,3-d]pyrimidine,

6-(4,4-dimethylcyclohexyl)-4-[(3,3-dimethylmorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine, or

1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-2,2-dimethylpiperidin-4-ol.

The group "1,1-dioxo-1λ^6-thiomorpholin-4-yl" means the same group as "1,1-dioxidothiomorpholin-4-yl".

[0033]

In the present specification, the "PAM" is a compound that binds to a receptor at a site different from a site for binding to an endogenous ligand, thereby improving the function of the receptor. The compound does not exhibit an agonistic activity alone, but has an action to increase the Potency and Efficacy of the receptor.

In the present specification, the "PAM action" is an action which the PAM as described above has. For example, in Test Example 1, it means a compound that left-shifts or up-shifts a GABA dose-response reaction curve having a horizontal axis as a dose and a vertical axis as a response. When a test drug has the "Potency", the compound left-

shifts the GABA dose-response curve leftwards, whereas when a test drug has "Efficacy", the compound up-shits GABA dose-response curve.

In the present specification, the symptoms of disease are not completely independent and may overlap each other. For example, the symptoms of schizophrenia, CIAS, and cognitive impairment may overlap each other.

Further, in the present specification, the name of disease is based on the references of "ICD10", which is the International Classification of Diseases of WHO (World Health Organization), 4th edition (DSM-4) and 5th edition (DSM-5) Statistical Manual of Mental Diagnosis in American Psychiatric Association (APA), and/or Guidelines of the Japanese Society of Neurology guidelines, or the like.

[0034]

The compound of the formula (I) may exist in the form of tautomers or geometrical isomers depending on the kind of substituents. In the present specification, the compound of the formula (I) may be described in only one form of isomer, yet the present invention includes such an isomer, isolated forms of the isomers, or a mixture thereof.

In addition, the compound of the formula (I) may have asymmetric carbon atoms or axial asymmetry in some cases, and correspondingly, it may exist in the form of optical isomers. The present invention includes an isolated form of the optical isomers of the compound of the formula (I) or a mixture thereof.

[0035]

Moreover, the present invention also includes a pharmaceutically acceptable prodrug of the compound represented by the formula (I). The pharmaceutically acceptable prodrug is a compound having a group that can be converted into an amino group, a hydroxyl group, a carboxyl group, or the like through solvolysis or under physiological conditions. Examples of the group forming the prodrug include the groups described in Progress in Medicine, 1985, p. 2157-2161 and "Pharmaceutical Research and Development" (Hirokawa Publishing Company) 1990, Vol. 7, Drug Design, p. 163-198.

[0036]

Moreover, the salt of the compound of the formula (I) is a pharmaceutically acceptable salt of the compound of the formula (I) and may form an acid addition salt depending on the kind of substituents. Specific examples thereof include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; and acid addition salts with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyltartaric acid, ditolyltartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, aspartic acid, and glutamic acid.

[0037]

The present invention further includes various hydrates or solvates, and polymorphic crystal substances of the compound of the formula (I) and a salt thereof. In addition, the present invention also includes compounds labeled with various radioactive or non-radioactive isotopes.

[0038]

(Preparation Methods)

The compound of the formula (I) and a salt thereof can be prepared using the characteristics based on the basic structure or the type of substituent thereof and by applying various known synthesis methods. At this time, depending on the type of the functional groups, it is effective in some cases, from the viewpoint of the preparation techniques, to substitute the functional group with an appropriate protective group (a group which is capable of being easily converted into the functional group), at the stage from starting materials to intermediates. Examples of such a protective group include those described in by P. G. M. Wuts and T. W. Greene, "Greene's Protective Groups in Organic Synthesis (4^{th} edition), 2006", and the like, and one of these may be appropriately selected and used as necessary depending on reaction conditions. In this kind of method, a desired compound can be obtained by introducing the protective group to carry out a reaction, and then by eliminating the protective group as necessary.

In addition, the prodrug of the compound of the formula (I) can be produced by introducing a specific group or by further carrying out the reaction using the obtained compound of the formula (I) at the stage from a starting material to an intermediate, just as in the case of the above-mentioned protective group. The reaction can be carried out using methods known to those skilled in the art, such as ordinary esterification, amidation, dehydration, and the like.

Hereinbelow, the representative preparation methods for the compound of the formula (I) will be described. Each of the production processes may also be carried out with reference to the References appended in the present description. Further, the preparation methods of the present invention are not limited to the examples as shown below.

[0039]

The following abbreviations may be used in some cases in the present specification, Examples, Preparation Examples, and Tables below.

PAM = positive allosteric modulator, PAM action = positive allosteric modulating action, CIAS = cognitive impairment associated with schizophrenia.

AcOH = acetic acid, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, brine = saturated physiological saline, CBB = Coomassie Brilliant Blue, CHAPS = 3-[(3-chloramidopropyl)dimethylammonio]propanesulfonate, DABCO = 1,4-

diazabicyclo[2.2.2]octane, DCE = 1,2-dichloroethane, DCM = dichloromethane, CDI = 1,1'-carbonyldiimidazole, D-MEM = Dulbecco's Modified Eagle's Medium, DIBAL = diisobutylaluminum, DIBOC = di-tert-butyl bicarbonate, DIPEA = N,N-diisopropylethylamine, DME = dimethoxyethane, DMF = N,N-dimethylformamide, DMSO = dimethylsulfoxide, DPPA = diphenylphosphoryl azide, DPPF = 1,1'-bis(diphenylphosphino)ferrocene, EGTA = glycol ether diamine tetraacetic acid, Et_2O = diethylether, EtOAc = ethyl acetate, EtOH = ethanol, GABA = γ-aminobutyric acid, HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridin-1-ium 3-oxide hexafluorophosphate, HCl/EtOAc = hydrogen chloride/EtOAc solution, HCl/dioxane = hydrogen chloride/dioxane solution, HBSS = Hanks' balanced salt solution, Hepes = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, HOBt = 1-hydroxybenzotriazole, IPE = diisopropylethylether, $KOBu^t$ = potassium tert-butoxide, LAH = lithiumaluminum hydride, MeCN = acetonitrile, MeOH = methanol, $MgSO_4$ = anhydrous magnesium sulfate, Ms = methanesulfonyl, MsCl = methanesulfonyl chloride, NaOEt = sodium methoxide, Na_2SO_4 = anhydrous sodium sulfate, $NaBH(OAc)_3$ = sodium triacetoxyborohydrie, $NaOBu^t$ = sodium tert-butoxide, NBS = N-bromosuccinimide, NCS = N-chlorosuccinimide, n-BuLi = n-butyllithium, NMO = N-methylmorpholine, NMP = N-methyl-2-pyrrolidone, ORF = open reading frame, $Pd(OAc)_2$ = palladium (II) acetate, Pd/C = palladium on carbon, Pd_2dba_3 = tris(dibenzylideneacetone) dipalladium (0), $Pd(PPh_3)_4$ = tetrakis(triphenylphosphine) palladium (0), Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, TEA = triethylamine, THF = tetrahydrofuran, TTIP = titanium (IV) isopropoxide, WSC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, silica gel column = silica gel column chromatography, basic silica gel column = basic silica gel column chromatography, supercritical chromatography = supercritical chromatography, saturated aqueous sodium bicarbonate = saturated aqueous $NaHCO_3$ solution.

[0040]

In the structural formulae, the following abbreviations may be used in some cases.

Ac = acetyl, Bn = benzyl, Boc = tert-butoxycarbonyl, Et = ethyl, Me = methyl, Ms = SO_2CH_3, Ph = phenyl, ^tBu or Bu^t = tert-butyl.

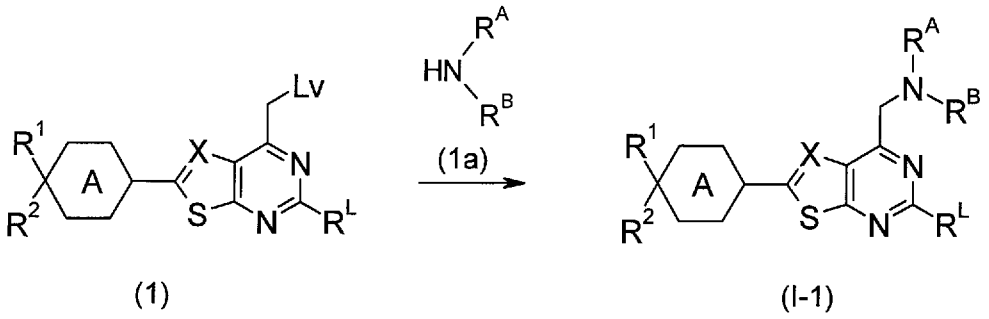
[0041]

Furthermore, for the sake of convenience, a concentration mol/L is expressed as M. For example, a 1 M aqueous NaOH solution means a 1 mol/L aqueous NaOH solution.

[0042]

(Production Process 1)

[Chem. 8]



(1) (I-1)

(In the formula, Lv represents a leaving group. The same shall apply hereinafter.)

The compound (I-1) of the present invention can be prepared from a compound (1) and a compound (1a).

The leaving group is, for example, halogen, an OMs group, or the like. This reaction can be carried out using the compound (1) and the compound (1a) in equivalent amounts, or with either thereof in an excess amount, by stirring a mixture thereof under any temperature condition from cooling to heating, preferably at 0°C to 80°C, usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction or without a solvent. The solvent is not particularly limited as long as it does not interfere with the reaction, but examples thereof include aromatic hydrocarbons such as toluene, xylene and the like, ethers such as Et_2O, THF, DME, dioxane and the like, halogenated hydrocarbons such as DCM, DCE, chloroform and the like, DMF, DMSO, EtOAc, MeCN, and a mixed solvent thereof. It may be advantageous in some cases for the smooth progress of the reaction to carry out the reaction in the presence of an organic base such as TEA, DIPEA, and NMO, or an inorganic base such as K_2CO_3, Na_2CO_3, and KOH.

[Documents]

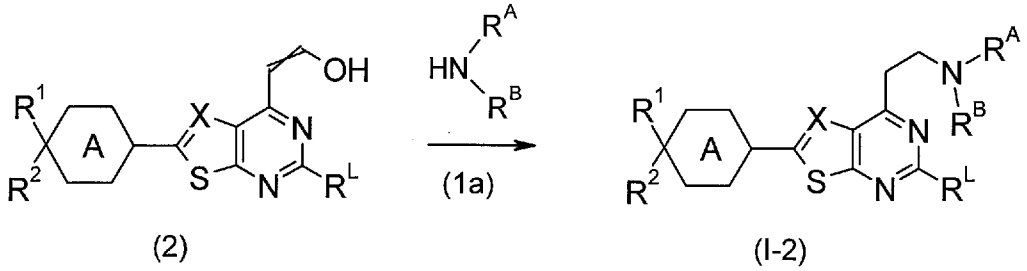
S. R. Sandler and W. Karo, "Organic Functional Group Preparations", 2nd edition, Vol. 1, Academic Press Inc., 1991

"Jikken Kagaku Koza (Courses in Experimental Chemistry) (5th edition)", Vol. 14 (2005), edited by The Chemical Society of Japan, Maruzen.

[0043]

(Production Process 2)

[Chem. 9]



(2) (I-2)

(In the formula, the crossing double bonds indicate a cis- or trans-configuration.)

The compound (I-2) of the present invention can be prepared from a compound (2) and the compound (1a).

In this reaction, the compound (2) and the compound (1a) are used in equivalent amounts, or with either thereof in an excess amount, and a mixture thereof is stirred under any temperature condition from -30°C to heating to reflux, preferably at 0°C to room temperature, usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of a reducing agent. The solvent is not particularly limited as long as it does not interfere with the reaction, but examples thereof include alcohols such as MeOH and the like, ethers, and a mixed solvent thereof. As the reducing agent, $NaBH(OAc)_3$, $NaBH_3CN$, $NaBH_4$, or the like can be used. It may be advantageous in some cases for the smooth progress of the reaction to add a dehydrating agent such as molecular sieves, AcOH, hydrochloric acid, a TTIP complex, or the like. By condensation of the compound (2) with the compound (1a), an imine is produced, and can be isolated as a stable intermediate in some cases. This imine intermediate can be subjected to reduction to prepare a compound (I-2). Further, instead of use of the reducing agent, a reduction catalyst (for example, Pd/C and a Raney nickel) can be used at normal pressure to 50 atm in a hydrogen atmosphere, in the presence or absence of an acid such as AcOH and hydrochloric acid in a solvent such as MeOH, EtOH, and EtOAc. This reaction can be carried out under any temperature condition from cooling to heating.

[Documents]

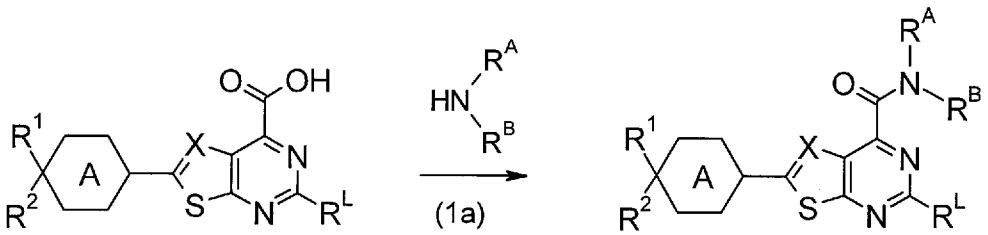
"Comprehensive Organic Functional Group Transformations II", A. R. Katritzky and R. J. K. Taylor, Vol. 2, Elsevier Pergamon, 2005

"Courses in Experimental Chemistry (5th edition)", edited by The Chemical Society of Japan, Vol. 14 (2005) (Maruzen)

[0044]

(Production Process 3)

[Chem. 10]



(3) (I-3)

The compound (I-3) of the present invention can be prepared from a compound (3) and the compound (1a).

In this reaction, the compound (3) and the compound (1a) are used in equivalent amounts, or with either thereof in an excess amount, and a mixture thereof is stirred under any temperature condition from cooling to heating, preferably at -20°C to 60°C, usually for 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of a condensing agent. The solvent is not particularly limited as long as it does not interfere with the reaction, but examples thereof include aromatic hydrocarbons, halogenated hydrocarbons such as DCM and the like, ethers, DMF, DMSO, EtOAc, CH_3CN, or water, and a mixed solvent thereof. The condensing agent is, for example, WSC, CDI, DPPA, HATU, phosphorous oxychloride, or the like. With an additive such as HOBt or the like, smooth progress of the reaction may be allowed in some cases. With an organic base such as pyridine, TEA, DIPEA, NMO or the like, or an inorganic base such as K_2CO_3, Na_2CO_3, KOH or the like, smooth progress of the reaction may be allowed in some cases.

Furthermore, the compound (I-3) of the present invention can also be prepared from a reactive derivative of a carboxylic acid (3) and the compound (1a). Examples of the reactive derivative include acid halides obtained by the reaction with a halogenating agent such as phosphorus oxychloride, thionyl chloride, and the like; mixed acid anhydrides obtained by the reaction with isobutyl chloroformate or the like; and active esters obtained by condensation with HOBt or the like. In the reaction of the reactive derivative with the compound (1a), a mixture thereof can be stirred under any temperature condition from cooling to heating, preferably at -20°C to 60°C usually for 0.1 hours to 5 days, with an organic base such as pyridine, TEA, DIPEA, NMO, and the like, in a solvent which is inert to the reaction. The solvent is not particularly limited as long as it does not interfere with the reaction, but halogenated hydrocarbons, aromatic hydrocarbons, ethers, or the like can be used. Further, the organic base can be used in combination with the solvent.

[Documents]

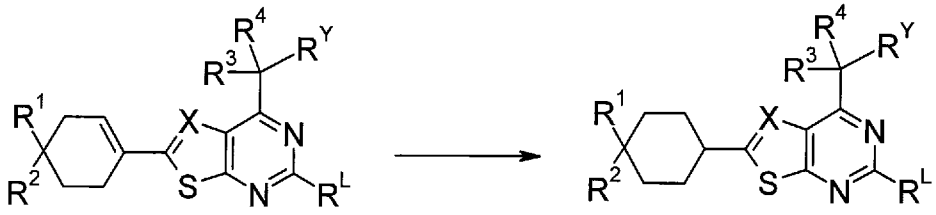
S. R. Sandler and W. Karo, "Organic Functional Group Preparations", 2nd edition, Vol. 1, Academic Press Inc., 1991

"Jikken Kagaku Koza (Courses in Experimental Chemistry) (5th edition)", Vol. 16 (2005), edited by The Chemical Society of Japan (Maruzen)

[0045]

(Production Process 4)

[Chem. 11]



(4) (I-4)

The compound (I-4) of the present invention can be prepared by the hydrogenation reaction of a compound (4).

In this reaction, the compound (4) is stirred under any temperature condition from cooling to heating, preferably at room temperature usually for 1 hour to 5 days, with a metal catalyst, in a solvent which is inert to the reaction under a hydrogen atmosphere. The solvent is not particularly limited as long as it does not interfere with the reaction, but examples thereof include alcohols, ethers, and the like. The metal catalyst is, for example, a palladium catalyst such as $Pd(OH)_2$ and the like. Instead of a hydrogen gas, formic acid or ammonium formate in equivalent amounts or in an excess amount can be used as a hydrogen source, relative to the compound (4).

[Documents]

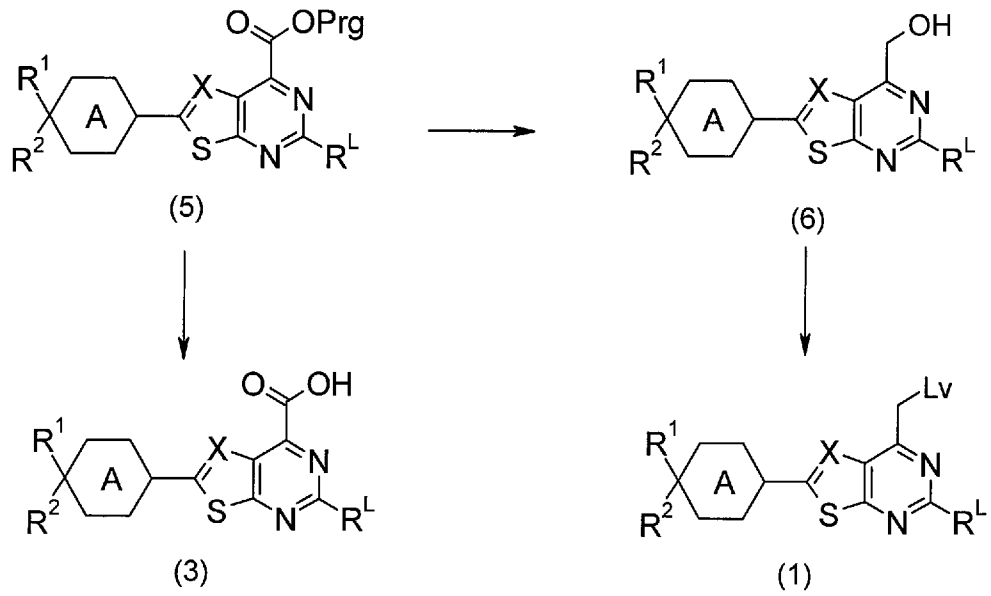
M. Hudlicky, "Reductions in Organic Chemistry, 2nd edition (ACS Monograph: 188)", ACS, 1996

"Jikken Kagaku Koza" (Courses in Experimental Chemistry) (5th edition), edited by The Chemical Society of Japan, Vol. 19 (2005) (Maruzen)

[0046]

(Starting Material Synthesis 1)

[Chem. 12]



(5) (6) (3) (1)

(In the formula, Prg means a protective group. The same shall apply hereinafter.)

[0047]

A starting compound (1) can be prepared from a compound (6).

(i) The starting compound (1) in which Lv is halogen can be prepared by the halogenations of a compound (6). This reaction can be carried out under any temperature condition from heating to heating to reflux with a halogenating agent such as SO_2Cl_2, phosphorous oxychloride or the like, and DMF. The solvent is not particularly limited as long as it does not interfere with the reaction, but toluene or the like can be used. As the halogenating agent, PBr_3, NBS, or the like can be used.

(ii) The starting compound (1) in which Lv is an OMs group can be prepared by adding an organic base and MsCl to the compound (6) under any temperature condition from 0°C to at room temperature in a solvent which is inert to the reaction under a hydrogen atmosphere. The solvent is not particularly limited as long as it does not interfere with the reaction, but DCM or the like can be used.

[0048]

The compound (6) can be prepared by the reduction of a compound (5).

In this reaction, the compound (5) is treated with a reducing agent in an equivalent amount or in an excess amount, under any temperature condition from cooling to heating, preferably at -20°C to 80°C, usually for 0.1 hours to 3 days, in a solvent which is inert to the reaction. The solvent is not particularly limited as long as it does not interfere with the reaction, but examples thereof include ethers, aromatic hydrocarbons, alcohols, and a mixed solvent thereof. As the reducing agent, $NaBH_4$, borane (BH_3), or a reducing agent in the following documents is used. When as the reducing agent, for example, $NaBH_4$ is used, calcium chloride may allow the smooth progress of the reaction in some cases.

[Documents]

M. Hudlicky, "Reductions in Organic Chemistry, 2nd edition (ACS Monograph: 188)", ACS, 1996

R. C. Larock, "Comprehensive Organic Transformations", 2nd edition, VCH Publishers, Inc., 1999

T. J. Donohoe, "Oxidation and Reduction in Organic Synthesis (Oxford Chemistry Primers 6)", Oxford Science Publications, 2000

"Jikken Kagaku Koza" (Courses in Experimental Chemistry) (5th edition), edited by The Chemical Society of Japan, Vol. 14 (2005) (Maruzen)

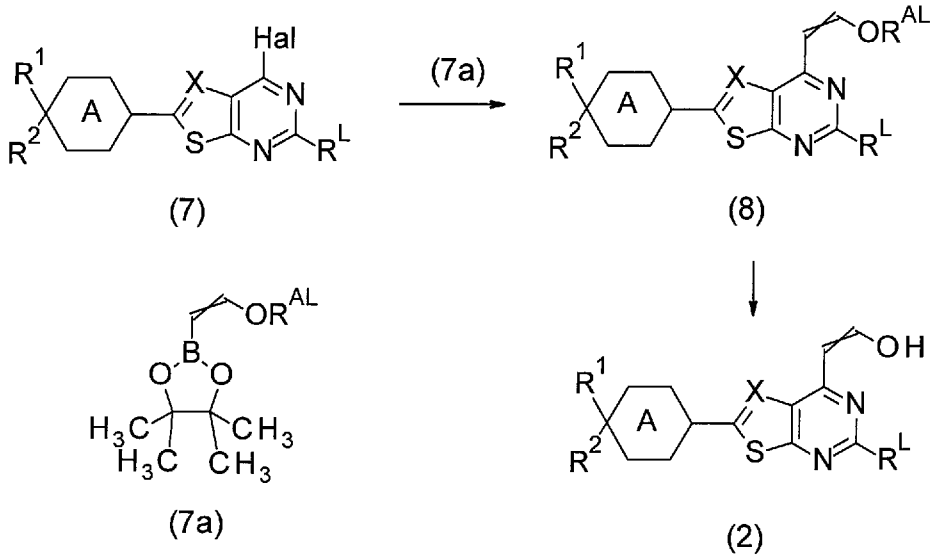
[0049]

The starting compound (3) can be prepared by the deprotection of the compound (5). This reaction can be carried out with reference to "Protective Groups in Organic Synthesis", Greene and Wuts, 3rd edition, John Wiley & Sons Inc, 1999.

[0050]

(Starting Material Synthesis 2)

[Chem. 13]



(In the formula, Hal represents halogen, R^{AL} represents lower alkyl, and $-OR^{AL}$ represents lower alkyloxy. The same shall apply hereinafter.)

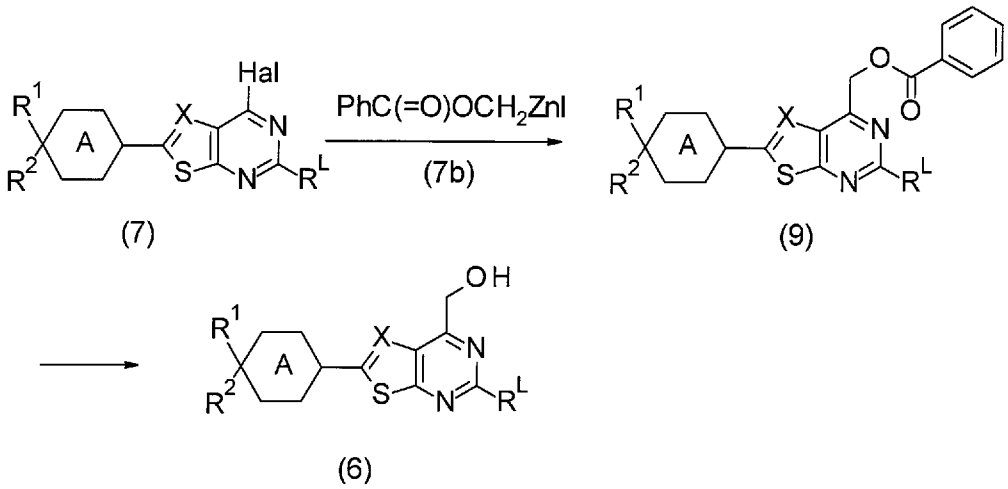
The compound (2) can be prepared by the deprotection of a compound (8). This reaction can be carried out with reference to "Protective Groups in Organic Synthesis", Greene and Wuts, 3rd edition, John Wiley & Sons Inc, 1999.

The compound (8) can be prepared from a compound (7) and a lower alkyloxyetheneboronic acid pinacol ester (7a). This reaction is a so-called Suzuki coupling between the compound (7) and a boronic acid compound. This reaction can be carried out by adding palladium, a phosphine ligand, and a metal base as a reagent under any temperature condition from at room temperature to heating to reflux. The solvent is not particularly limited as long as it does not interfere with the reaction, but a solvent which is inert to the reaction, such as aromatic hydrocarbons, ethers, halogenated hydrocarbons, aprotic solvents, and AcOH may be used or a solvent may not be used. As the palladium, for example, $Pd(OAc)_2$, Pd_2dba_3, or the like can be used. As the phosphine ligand, for example, BINAP, DPPF, $P(Bu^t)_3$, or the like can be used. As the metal base, K_2CO_3, Cs_2CO_3, $NaOBu^t$, or the like can be used.

[0051]

(Starting Material Synthesis 3)

[Chem. 14]



The starting compound (6) can be prepared by the hydrolysis of a compound (9).

The compound (9) can be prepared from the compound (7) and a compound (7b). This reaction is Negishi coupling, in which an organic zinc compound and an organic halide are condensed with a palladium or nickel catalyst to prepare a carbon-carbon bonding product. The solvent is not particularly limited as long as it does not interfere with the reaction, but THF or the like can be used. As the catalyst, for example, $Pd(PPh_3)_4$ can be used. Usually, the reaction can be carried out at room temperature.

[Documents]

Negishi, E. Acc. Chem. Res. 1982, vol. 15, p. 340-348,

"Metal-Catalyzed Cross-Coupling Reactions", edited by A. de Meijere and F. Diederich, 2nd edition, VCH Publishers Inc., 2004,

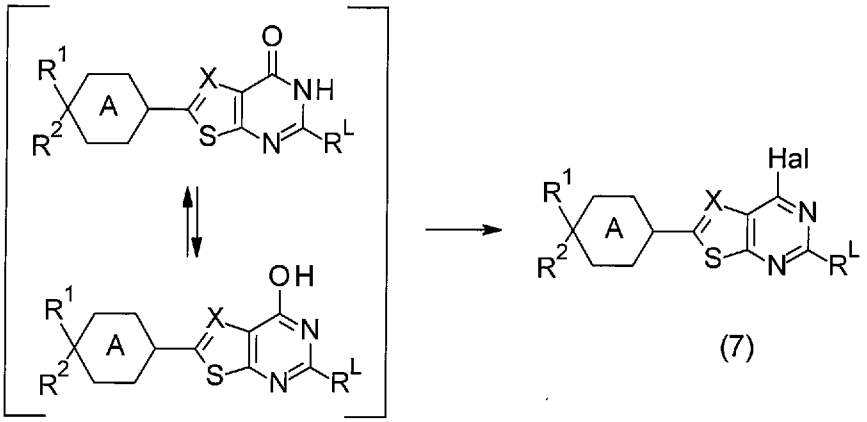
"Jikken Kagaku Koza" (Courses in Experimental Chemistry) (5th edition), edited by The Chemical Society of Japan, Vol. 13 (2005) (Maruzen)

Organic Letters, 2004, p. 3225, Synlett, 2008, p. 543

[0052]

(Starting Material Synthesis 4)

[Chem. 15]



(10)

(7)

(The compound (10) is present as a tautomer as a ketoenol as described above. In the present specification, the compound (10) and Preparation Example Pr 23 and so on as described below, for the sake of convenience, are denoted by either of a keto form or an enol form.)

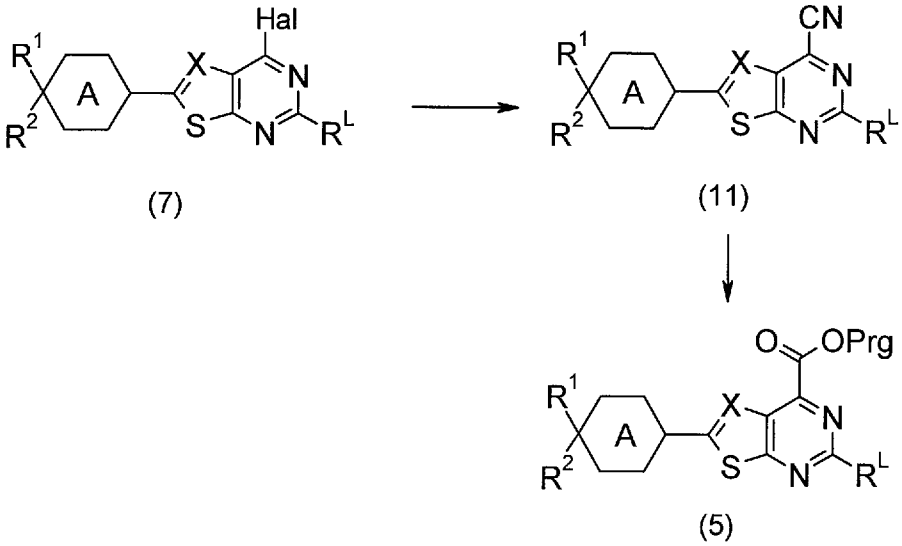
The compound (7) can be prepared by the halogenations of the compound (10).

This reaction can be carried out in the same manner as the method described in Starting Material Synthesis 1 above.

[0053]

(Starting Material Synthesis 5)

[Chem. 16]



(7)

(11)

(5)

The starting compound (5) can be prepared from a compound (11). Prg is lower alkyl such as Me and Et.

This reaction can be carried out by using an alcohol (Prg-OH) as a solvent and a reagent, and stirring a mixture thereof with a compound (11) and hydrogen hydride such as

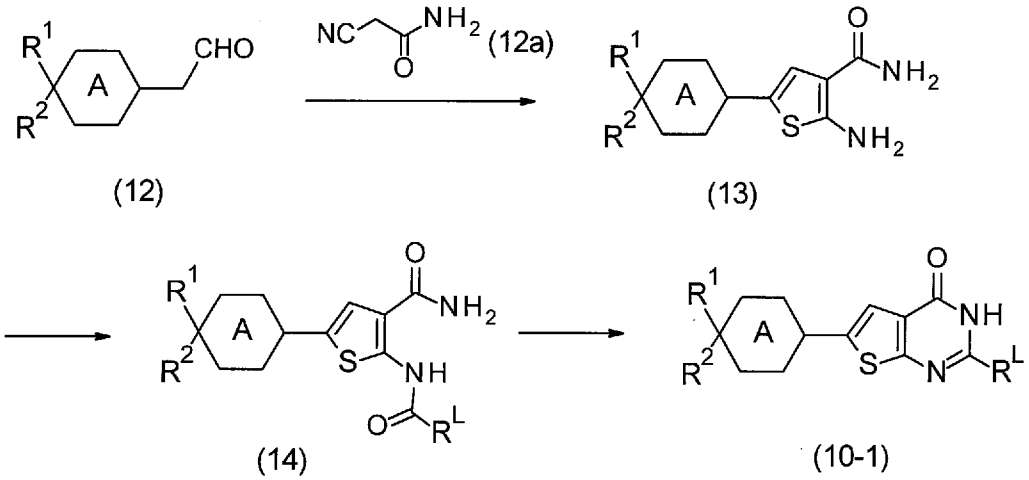
HCl/dioxane and HCl/EtOAc, under any temperature condition from room temperature to heating, for several hours to overnight.

The compound (11) can be prepared by the cyanation of the compound (7). This reaction can be carried out with a CN source such as NaCN, KCN, Zn $(CN)_2$ or the like, and CH_3SO_2Na or the like, under any temperature condition from 50°C to 80°C, for several hours to overnight under stirring. The solvent is not particularly limited as long as it does not interfere with the reaction, but DMF or the like can be used.

[0054]

(Starting Material Synthesis 6)

[Chem. 17]



The starting compound (10-1) can be prepared from a compound (14).

This reaction can be carried out by heating and stirring the compound (14) with an aqueous inorganic base solution such as an aqueous NaOH solution or the like, in a solvent which is inert to the reaction. The solvent is not particularly limited as long as it does not interfere with the reaction, but alcohols such as EtOH and the like can be used.

The compound (14) can be prepared from a compound (13).

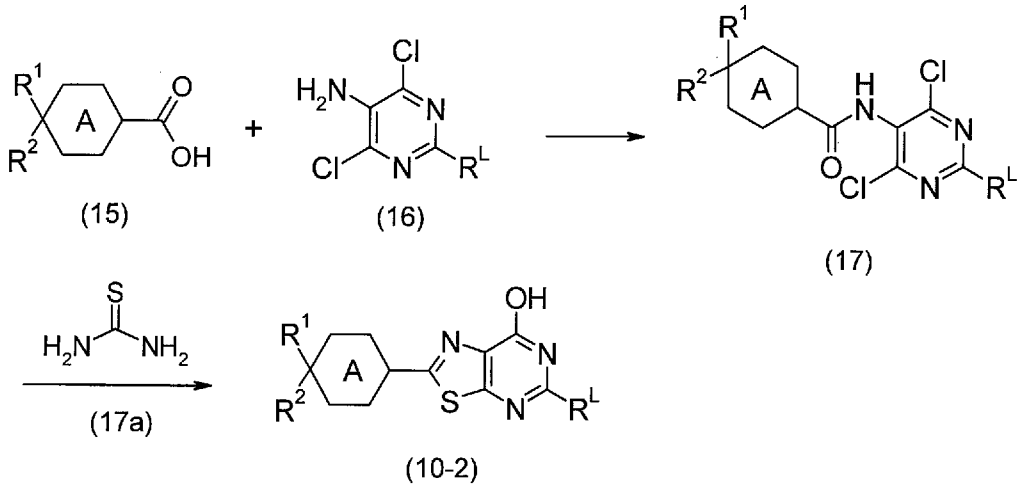
This reaction is amidation in which the compound (13) is reacted with an acid halide of a formula R^L-C(C=O)-Hal. For the reaction, the same method as Production Process 3 can be used.

The compound (13) can be prepared from the compound (12) with an organic base such as 2-cyanoacetamide (12a), sulfur, TEA, and the like in a solvent, usually by heating. The solvent is not particularly limited as long as it does not interfere with the reaction, but DMF or the like can be used.

[0055]

(Starting Material Synthesis 7)

[Chem. 18]



(15) (16) (17)

(17a) (10-2)

The starting compound (10-2) can be prepared from a compound (17) and a compound (17a).

This reaction can be carried out by adding formic acid to the compound (17) and the compound (17a), in a solvent which is inert to the reaction, and heating and stirring. The solvent is not particularly limited as long as it does not interfere with the reaction, but an alcohol or the like can be used.

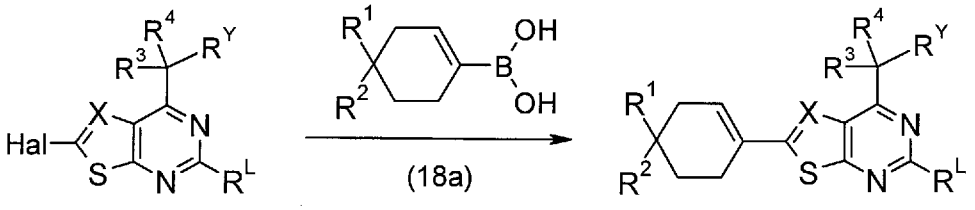
The compound (17) can be prepared by the amidation of the compound (15) and the compound (16).

This reaction can be carried out in the same manner as the method described in Production Process 3.

[0056]

(Starting Material Synthesis 8)

[Chem. 19]



(18) (18a) (4)

[0057]

The starting compound (4) can be prepared from a compound (18) and a compound (18a).

This production process is a so-called Suzuki coupling, and can be carried out in the same manner as the method for preparing the compound (7) from the compound (8) of Starting Material Synthesis 2 as described above.

[0058]

The compound of the formula (I) is isolated and purified as a free compound, a salt, a hydrate, a solvate, or a polymorphic crystal substance thereof. A salt of the compound of the formula (I) can be prepared by carrying out a conventional salt forming reaction.

Isolation and purification are carried out by employing ordinary chemical operations such as extraction, fractional crystallization, various types of fractional chromatography, and the like.

Various isomers can be prepared by selecting an appropriate starting compound or separated by using the difference in the physicochemical properties between the isomers. For example, the optical isomers can be obtained by means of a general method for designing optical resolution of racemic compounds (for example, fractional crystallization for inducing diastereomer salts with optically active bases or acids, chromatography using a chiral column or the like, and others), and further, the isomers can also be prepared from an appropriate optically active starting material.

[0059]

The pharmacological activity of the compound of the formula (I) or a salt thereof was confirmed by the tests below.

[0060]

(Materials)

The medium composition and the buffer composition used in the following Test Examples are shown below (the concentration of each reagent represents a final concentration).

KH Buffer (Krebs-Henseleit Buffer): Aqueous solution containing 119 mM NaCl, 4.8 mM KCl, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 25 mM $NaHCO_3$, 10 mM Glucose, and 20 mM Tris-HCl (pH = 7.4).

A Buffer: Aqueous solution containing 0.32 M sucrose, 1 mM $MgCl_2$, and 1 mM K_2HPO_4.

B Buffer: Aqueous solution containing 50 mM Tris-HCl (pH = 7.7), 100 mM NaCl, 10mM $MgCl_2$, 2 mM $CaCl_2$, 0.2 mM EGTA, and 30 μM GDP.

C Buffer: Aqueous solution containing 20 mM Tris-HCl (pH = 7.7) and 5 mM $MgCl_2$.

Base buffer: Aqueous solution containing 2.5 mM probenecid, 20 mM Hepes-NaOH (pH = 7.5), and a Hanks' balanced salt solution (HBSS) containing 0.02% CHAPS.

Fluo-4 loaded solution: Base buffer containing 1 μM Fluo-4 AM (Dojindo Molecular Technologies, Inc.), 0.067% DMSO and 0.0033% Pluronic F-127 (Life Technologies).

[0061]

Test Example 1: Confirmation of PAM action by GTPγS binding test

The function of the $GABA_B$ receptor of the compound of the present invention was evaluated using a [^{35}S] GTPγS binding test. This method is used for the detection of the PAM action of the compound on the $GABA_B$ receptor (Journal of Pharmacology and Experimental Therapeutics, 2003, vol. 307(1), p. 322-330; and Molecular Pharmacology, 2001, vol. 60(5), p. 963-971).

[0062]

(Membrane Preparations)

The mouse brain cortical membrane was prepared with reference to a method for preparing a rat brain membrane (European Journal of Pharmacology, 1990, vol. 187 (1), p. 27-38).

The cortex (about 30 g) was cut out of the brains of 90 ddY mice (Japan SLC, Inc.). An A buffer was added to the cortex (cortex/A buffer = about 1:3 (wt/vol)), and homogenized with a glass Teflon-lined homogenizer (Teflon: registered trademark) on ice. The homogenate was centrifuged (750 g, 10 min, 4°C) and a supernatant was then obtained. An A buffer (90 mL) was added to pellets and homogenized on ice, and a supernatant (750 g, 10 min, 4°C) was then obtained. By repeating this operation, the supernatant was collected.

The supernatant was centrifuged (18000 g, 15 min, 4°C). Ultrapure water (54 mL) was added to the pellets, left to stand for 30 min on ice, and then centrifuged (39000 g, 20 min, 4°C). The pellets were suspended in a KH buffer (54 mL), repeatedly frozen and thawed, and centrifuged (18000 g, 15 min) at 4°C. The buffer was added to the pellets and then frozen and thawed, and this operation was repeated until the centrifugation. By a Bradford method using a protein assay (Protein assay CBB solution; Nacalai Tesque, Inc.), a KH buffer suspension of the pellet was prepared at a protein concentration of 10 mg/mL.

[0063]

(GTPγS Binding Test)

The PAM action of the $GABA_B$ receptor in the mouse brain cortex of a test drug was evaluated. To each of wells of a 96-well microplate, a test drug diluted with a B buffer at each concentration (3 nM to 30 μM), a mouse brain cortex membrane (4 μg), [^{35}S] GTPγS (final concentration of 0.34 nM, Muromachi Yakuhin Co., Ltd.; Institute of Isotopes Co., Ltd.), GABA (final concentration of 0.3 μM; Sigma) were added in this order, followed by standing at room temperature for 1 hour. With a harvester (Filtermate, Perkin-Elmer, Inc.), the suspension was suction-filtered through a glass filter (UniFilter 96-well GF/B filter plates, Perkin-Elmer, Inc.). The glass filter was washed with a C buffer that had been ice-cooled. After drying the glass filter, a liquid scintillation cocktail (50 μL, MicroScinti-PS; PerkinElmer, Inc.) was added to each well. The amount of [^{35}S]

GTPγS bound to the membrane was measured on a plate reader (TopCount, PerkinElmer, Inc.).

[0064]

(Data Analysis)

The maximum reaction rate of 100 μM GABA was taken as 100%. The reaction rate when GABA and the test drug did not exist was taken as 0%. At a time when the test drug was not added, the concentration of the test drug that increased the reaction rate from 20% with 0.3 μM GABA to 50% was taken as a PAM Potency (μM) of the $GABA_B$ of the test drug. In the presence of 0.3 μM GABA, the maximum reaction rate of the effect on the $GABA_B$ receptor when the test drug was administered up to maximum 30 μM was taken as a PAM Efficacy (%) of the $GABA_B$ of the test drug.

[0065]

The Potency and Efficacy of several representative Example Compounds of the present invention are shown in Table below (In the Table, Ex represents Example Compound No. The "Potency" represents the PAM Potency of $GABA_B$ of the test drug, and the "Efficacy" represents PAM Efficacy (%) of $GABA_B$ of the test drug. These shall apply hereinafter).

[0066]

[Table 1]

No.	Potency (μM)	Efficacy (%)	No.	Potency (μM)	Efficacy (%)
Ex2	0.11	207	Ex55	0.25	175
Ex4	0.20	161	Ex61	0.24	160
Ex5	0.24	176	Ex72	0.089	289
Ex7	0.24	139	Ex73	0.085	272
Ex12	0.23	377	Ex74	0.19	244
Ex31	0.11	300	Ex79	0.046	230
Ex31-1	0.18	191	Ex101	0.38	134
Ex39	0.42	165	Ex102	0.40	127
Ex40	0.53	203	Ex104	0.079	218
Ex43	0.26	118	Ex108	0.20	176
Ex44	0.27	119	Ex127	0.11	338
Ex45	0.44	134	Ex132	0.15	218
Ex46	0.18	188	Ex142	0.0071	214
Ex47	0.12	240	Ex143	1.2	182
Ex48	0.26	238	Ex144	0.31	182
Ex50	0.54	222	Ex146	0.10	258
Ex51	0.15	249	Ex151	0.12	168
Ex52	0.17	259	Ex153	0.059	180
Ex54	0.32	88	Ex155	0.046	159

[0067]

Test Example 2: Confirmation of PAM Action Using Cells That Stably Express $GABA_B$ Receptor

A natural $GABA_B$ receptor has a heterodimeric structure consisting of two kinds of subunits of $GABA_{B1}$ and $GABA_{B2}$ (Nature, 1997, vol. 386, p. 239-246) In the subunit of $GABA_{B1}$, two major splice variants referred to as $GABA_{B1a}$ and $_{1b}$ exist. However, the two variants have no difference in the pharmacological effects in the receptor-downstreaming signals (Nature, 1998, vol. 396, p. 683-687).

In HEK293 cells expressing the heterodimers of $GABA_{B1b}$ and $GABA_{B2}$, the PAM action in the presence of GABA was measured over time with a change in the intracellular Ca^{2+} concentration using RFU (relative fluorescence units) as an index, and evaluated.

[0068]

(Establishment of Cell Lines Expressing $GABA_B$ Receptors)

All vectors, wherein each vector was formed by human $GABA_{B1b}$ (NM_021903. 2), $GABA_{B2}$ (NM_005458. 7), or Gαqo chimera, were incorporated by lipofection to establish stably expressing human embryonic kidney-derived cell lines, HEK293 cells (ATCC).

The Gαqo chimera was fabricated by the following method. The genes coding human Gαq (NM_002072.3) were cloned, and C-terminal 15 base pairs (1107-1121 bp) of ORF (41-1121 bp) of Gαq was substituted with C-terminal 15 base pairs (1948-1962 bp) of ORF (898-1962 bp) of human Gαo (NM_138736. 2) into a Gαqo chimera.

[0069]

(Measurement of Intracellular Calcium Mobilization Due to $GABA_B$ Receptor Activation by FLIPR)

A change in the intracellular concentration of calcium mobilized due to activation of a $GABA_B$ receptor was measured with a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices). The stably expressing cells established as described above were proliferated in a D-MEM medium containing a screening agent (0.5 mg/mL G418 Disulfate and 0.2 mg/mL Hydromycin B solution), 1% penicillin/streptomycin, and 10% FCS. About 1×10^4 cells/well were diluted and seeded in a black-wall, 384-well poly-D-lysin-coated plate (Becton Dickinson) in a D-MEM medium containing 10% FCS, but not a selective agent and 1% penicillin/streptomycin. After 24 hours, the medium was removed from the plate, and a Fluo-4 loaded solution (20 μL) was added to each well, followed by incubation at room temperature for 2 hours. The fluorescent reagent loaded solution was removed from each well, the cells were washed with a base buffer three times, and then a base buffer (20 μL) was added thereto, followed by analysis with FLIPR TETRA (Molecular Devices). The base buffer (10 μL) solution of the test drug was added thereto to a final concentration (1 nM to 30 μM) and the measurement of a change in

the fluorescence was initiated. Thereafter, GABA (1 μM, 20 μL) was added thereto and the measurement was continued. The change in the fluorescence was measured every two or five seconds.

[0070]

(Data Analysis)

The maximum reaction rate of 100 μM GABA was taken as 100%. The reaction rate when GABA and the test drug did not exist was taken as 0%. At a time when the test drug was not added, the concentration of the test drug that increased the reaction rate from 5% with 1 μM GABA to 50% was taken as a PAM Potency (μM) of the $GABA_B$ of the test drug. In the presence of 1 μM GABA, the maximum reaction rate of the effect on the $GABA_B$ receptor when the test drug was administered up to maximum 30 μM was taken as a PAM Efficacy (%) of the $GABA_B$ of the test drug.

[0071]

The evaluation test results in FLIPR of several representative Example Compounds of the present invention are shown in Table below.

[0072]

[Table 2]

No.	Potency (μM)	Efficacy (%)
Ex2	0.059	470
Ex31	0.22	273

[0073]

Test Example 3: Y-Maze Test: Improvement Effect on Cognitive impairment

The effect on the improvement of short-term memory impairment of the compound of the present invention was evaluated using a Y-maze test that is an experimental system of spontaneous alternation behavior.

[0074]

(Experiment Device)

As the Y maze, a maze, in which three runways having a length of one arm of 40 cm, a height of a wall of 13 cm, a width of a floor of 3 cm, and a width of a top of 10 cm are each joined at 120 degrees in a Y shape, was used.

[0075]

(Test Method)

The test drugs were orally administered once to 5- to 6-week old ddY male mice (n=8) at 30 minutes before the initiation of the Y-maze test, and further, MK-801 (Sigma) which is an NMDA receptor antagonist inducing cognitive impairment was intraperitoneally administered thereto at a dose of 0.15 mg/kg at 20 minutes before the initiation of the Y-maze test.

Further, for the mice in a control group, a vehicle (0.5% methyl cellulose) was used instead of the test drug, and physiological saline was used instead of MK-801.

For the mice in the MK-801 control group, a vehicle (0.5% methyl cellulose) was used instead of the test drug.

The mouse was placed at one end of a certain place in the runway in the Y maze, and then freely explored for 8 minutes, and the runways into which the mice invaded and the order thereof were recorded. The number of the entries of the mice within a measurement time was counted and defined as a total number of entries. Among these, a combination when the mice invaded into different three runways (for example, in a case where the three arms are referred to as a, b, and c, respectively, and the order of the arms with entries is abccbacab, the number was counted as 4, including the repetition) was defined as the number of spontaneous alternation behaviors. For the spontaneous alternation rate, a spontaneous alternation rate calculated by the following equation was taken as an index of spontaneous alternation behavior:

Spontaneous alternation rate = number of spontaneous alternation behaviors/(total number of entries – 2) × 100.

A higher value of this index indicates that more short-term memory is retained.

[0076]

(Data Analysis)

The measured value was expressed in an average value ± a standard error. A significant difference assay between the control group and the MK-801 control group was carried out by a Student's t-test. Further, a Dunnett's multi-comparison test was carried out in a significant difference assay between the group administered with the test drug and the MK-801 control group, and it was thus determined that the test drug has an action to improve the learning disorder. In each test, if $p < 0.05$ was satisfied, it was determined that there was a significant difference.

[0077]

The MED (mg/kg) of several representative Example Compounds in the present invention are shown in Table below.

[0078]

[Table 3]

No.	MED (mg/kg)
Ex2	0.1
Ex31	1.0

[0079]

Test Example 4: Effect on Pressure Pain Threshold in Model with Reserpine-Induced Muscle Pain

This model is a model that mimics the pathological conditions of fibromyalgia. This test was carried out on the basis of the description in Pain, 2009, vol. 146, p. 26-33.

Reserpine (1 mg/kg) was subcutaneously administered to the male SD rat (Japan SLC, Inc.)) once per day for 3 days. After 5 days, the solvent or the test drug was orally administered. After 30 minutes, the pressure pain threshold value was measured using a Randall-Selitto instrument (Muromachi Kikai Co., Ltd.) in the gastrocnemius muscle. The significant difference assay between the solvent group and the group administered with the test drug was carried out by comparison between the groups using a Student's t-test or a Dunnett's multiple comparison test. Here, the value obtained by administering a solvent to a normal rat not administered with reserpine was taken as 100%, and the value of the reserpine group administered with a solvent was taken as 0%. In each assay, if $p < 0.05$ was satisfied, it was determined that there was a significant difference.

[0080]

[Table 4]

No.	MED (mg/kg)
Ex2	0.03

[0081]

As a result of the tests above, it was found that the compound of the present invention has a PAM action of the $GABA_B$ receptor. Accordingly, the compound is useful for preventing or treating $GABA_B$ receptor -related diseases or disorders, for example, schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, Charcot-Marie-Tooth disease, or the like.

[0082]

A pharmaceutical composition containing one or two or more kinds of the compound of the formula (I) or a salt thereof as an active ingredient can be prepared using excipients that are usually used in the art, that is, excipients for pharmaceutical preparation, carriers for pharmaceutical preparation, and the like according to the methods usually used.

Administration can be accomplished either by oral administration via tablets, pills, capsules, granules, powders, solutions, and the like, or parenteral administration injections, such as intraarticular, intravenous, or intramuscular injections, and the like, suppositories, ophthalmic solutions, eye ointments, transdermal liquid preparations, ointments, transdermal patches, transmucosal liquid preparations, transmucosal patches, inhalers, and the like.

[0083]

As the solid composition for oral administration, tablets, powders, granules, or the like are used. In such a solid composition, one or more active ingredient(s) are mixed with at least one inactive excipient. In a conventional method, the composition may contain inactive additives, such as a lubricant, a disintegrating agent, a stabilizer, or a

solubilization assisting agent. If necessary, tablets or pills may be coated with sugar or a film of a gastric or enteric coating substance.

The liquid composition for oral administration contains pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, or the like, and also contains generally used inert diluents, for example, purified water or ethanol. In addition to the inert diluent, the liquid composition may also contain auxiliary agents, such as a solubilization assisting agent, a moistening agent, and a suspending agent, sweeteners, flavors, aromatics, and antiseptics.

[0084]

The injections for parenteral administration include sterile aqueous or non-aqueous solution preparations, suspensions and emulsions. The aqueous solvent includes, for example, distilled water for injection and physiological saline. Examples of the non-aqueous solvent include alcohols such as EtOH. Such a composition may further contain a tonicity agent, an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizing agent, or a solubilizing aid. These are sterilized, for example, by filtration through a bacteria retaining filter, blending of a bactericide, or irradiation. In addition, these can also be used by preparing a sterile solid composition, and dissolving or suspending it in sterile water or a sterile solvent for injection prior to its use.

[0085]

Examples of the agent for external use includes ointments, plasters, creams, jellies, patches, sprays, lotions, eye drops, eye ointments, and the like. The agents contain generally used ointment bases, lotion bases, aqueous or non-aqueous liquid preparations, suspensions, emulsions, or the like.

[0086]

As the transmucosal agents such as an inhaler, a transnasal agent, and the like, those in the form of a solid, liquid, or semi-solid state are used, and can be prepared in accordance with a conventionally known method. For example, a known excipient, and also a pH adjusting agent, an antiseptic, a surfactant, a lubricant, a stabilizing agent, a thickening agent, or the like may be appropriately added thereto. For the administration, an appropriate device for inhalation or blowing can be used. For example, a compound may be administered alone or as a powder of formulated mixture, or as a solution or suspension in combination with a pharmaceutically acceptable carrier, using a conventionally known device or sprayer, such as a measured administration inhalation device, and the like. A dry powder inhaler or the like may be for single or multiple administration use, and a dry powder or a powder-containing capsule may be used. Alternatively, this may be in a form such as a pressurized aerosol spray which uses an appropriate ejection agent, for example, a suitable gas such as chlorofluoroalkane, carbon dioxide, and the like, or other forms.

[0087]

In general oral administration, the daily dose is suitably from about 0.001 mg/kg to 100 mg/kg, preferably from 0.1 mg/kg to 30 mg/kg, and more preferably from 0.1 mg/kg to 10 mg/kg, per body weight, administered in one portion or in 2 to 4 divided portions. In the case of intravenous administration, the daily dose is suitably from about 0.0001 mg/kg to 10 mg/kg per body weight, once a day or two or more times a day. In addition, a transmucosal agent is administered at a dose from about 0.001 to 100 mg/kg per body weight, once a day or two or more times a day. The dose is appropriately decided in response to the individual case by taking the symptoms, the age, and the gender, and the like into consideration.

[0088]

Although varying depending on administration routes, dosage forms, administration sites, or the types of excipients and additives, the pharmaceutical composition of the present invention contains 0.01% by weight to 100% by weight, and in a certain embodiment, 0.01% by weight to 50% by weight of one or more kinds of the compound of the formula (I) or a salt thereof, which is an active ingredient.

[0089]

The compound of the formula (I) can be used in combination with various agents for treating or preventing the diseases for which the compound of the formula (I) is considered to be effective. The combined preparation may be administered simultaneously, or separately and continuously, or at a desired time interval. The preparations to be co-administered may be a blend, or may be prepared individually.

Examples

[0090]

Hereinbelow, the preparation methods for the compound of the formula (I) will be described in more detail with reference to Examples. Further, the present invention is not limited to the compounds described in the Examples as described below. Furthermore, the production processes for the starting compounds will be described in Preparation Examples. Further, the preparation methods for the compound of the formula (I) are not limited to the preparation methods of the specific Examples as below, but the compound of the formula (I) can be prepared by any combination of the preparation methods or the methods that are apparent to a person skilled in the art.

[0091]

The compounds shown in the following Table were prepared by using the above-mentioned preparation methods and the methods that are apparent to a person skilled in the art, or modified methods thereof. The tables show the structures and physicochemical

data of the Example Compounds and methods for preparing the compounds. Further, the symbols in the tables represent the following meanings.

No. = Example No. or Preparation Example No.

No./Inf = (Example No. or Preparation Example No. of the compound)/(salt information of the compound). /Inf, for example, /HCl denotes that the Example Compound is a monohydrochloride. Further, a case where /2HCl is described means that the compound is a dihydrochloride. In addition, /FUM denotes that the compound is fumarate. A case where nothing is described indicates that the compound is a free form. In the tables, Chiral denotes that the compound is an optically active form.

Pr = Preparation Example No., Ex = Example No., Ref = preparation method (the numeral shows that the Example Compound was prepared by the same preparation method as that for a compound having its number as the Example No. Further, in the tables, for example, in Ex86, a case where Pr8 + Ex85 is described denotes that a material is prepared by the same method as for the preparation of Preparation Example Compound 8 (Pr8), and then, by using the obtained material as starting material. A desired product is prepared by the same method as for the preparation of Example Compound 85 (Ex85). Further, in Tables, for example, in Pr26, a case where Pr8 + Ex1 is described denotes that a material is prepared by the same method as for the preparation of Preparation Example Compound 8 (Pr8), and then, by using the obtained material as starting material. A desired product is prepared by the same method as for the preparation of Example Compound 1 (Ex1)).

Str = Structural formula, Data = Physicochemical data.

NMR ($CDCl_3$) = Chemical shift δ value in ^{1}H-NMR, as measured using $CDCl_3$ as a solvent, NMR (DMSO-d_6) = Chemical shift δ value in ^{1}H-NMR, as measured using DMSO-d_6 as a solvent, EI = m/z value measured by EI-MS, ESI = m/z value measured by ESI-MS, APCI = m/z value measured by APCI-MS, APCI/ESI = m/z value measured by APCI and ESI at once, CI = m/z value measured by CI-MS. Further, in a case where + or – is described as a suffix in ESI or the like, + means a MS value measured in a positive ion mode and – means a MS value measured in a negative ion mode.

[0092]

Preparation Example 3

To a mixture of 2-acetamide-5-(4,4-dimethylcyclohexyl)thiophene-3-carboxamide (37.3 g) and EtOH (200 mL) was added a 2 M aqueous NaOH solution (200 mL), followed by heating and stirring at 80°C for 2 hours. The reaction mixture was left to be cooled to room temperature, and then, 1 M hydrochloric acid (500 mL) was added thereto, followed by stirring at room temperature. The precipitate was collected by filtration to obtain 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4(3H)-one (26.3 g).

[0093]

Preparation Example 4

To a mixture of 6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4(3H)-one (25.0 g) and toluene (300 mL) were added phosphorous oxychloride (14 mL) and DMF (200 μL), followed by heating to reflux at 150°C for 14 hours. The reaction mixture was left to be cooled to room temperature and concentrated under reduced pressure. To the residue were added chloroform, water, and saturated aqueous sodium bicarbonate, followed by stirring. The reaction mixture was extracted with chloroform. The organic layer was washed sequentially with water and brine. To the organic layer were added $MgSO_4$, activated carbon (2 g), and silica gel (100 mL), followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain 4-chloro-6-cyclohexyl-2-methylthieno[2,3-d]pyrimidine (27.4 g).

[0094]

Preparation Example 4-1

To a mixture of 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4(3H)-one (30.0 g) and toluene (240 mL) were added phosphorous oxychloride (40 mL) and DMF (1.0 mL), followed by heating to reflux at 130°C for 2 hours. The reaction mixture was left to be cooled to room temperature and concentrated under reduced pressure. To the residue were added chloroform and saturated aqueous sodium bicarbonate, followed by stirring. The organic layer was washed sequentially with water and brine. To the organic layer were added $MgSO_4$, activated carbon (10 g), and silica gel (100 mL), followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain 4-chloro-6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine (31.3 g).

[0095]

Preparation Example 4-6

To a mixture of 2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-ol (16.2 g) and toluene (160 mL) were added DMF (10 mL) and phosphorous oxychloride (11 mL), followed by stirring at 95°C for 30 minutes. The reaction mixture was concentrated under reduced pressure. To the residue was added chloroform, and the mixture was neutralized with a 1 M aqueous NaOH solution in an ice bath and extracted with chloroform. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc) to obtain 7-chloro-2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidine (13.2 g).

[0096]

Preparation Example 5

To a mixture of 4-chloro-6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine (31.1 g) and DMF (220 mL) were added CH_3SO_2Na (11 g) and KCN (10 g), followed by heating and stirring at 70°C for 15 hours. The reaction mixture was

concentrated to about a half of the amount under reduced pressure, diluted with water (300 mL), and then stirred. The precipitate was collected by filtration. To the precipitate was added chloroform, followed by dissolving therein, and $MgSO_4$, activated carbon (10 g), and silica gel (100 mL) were added thereto, followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine-4-carbonitrile (27.4 g).

[0097]

Preparation Example 6

To a mixture of 6-cyclohexyl-2-methylthieno[2,3-d]pyrimidine-4-carbonitrile (23.5 g) and EtOH (100 mL) was added 4 M HCl/dioxane (100 mL), followed by stirring at 80°C for 2 days. The reaction mixture was left to be cooled to room temperature and concentrated under reduced pressure. To the residue was added chloroform, followed by dissolving therein, and activated carbon (2 g) and basic silica gel (100 mL) were further added thereto, followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain ethyl 6-cyclohexyl-2-methylthieno[2,3-d]pyrimidine-4-carboxylate (30.8 g).

[0098]

Preparation Example 6-1

To a mixture of 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine-4-carbonitrile (27.4 g) and EtOH (200 mL) was added 4 M HCl/dioxane (200 mL), followed by stirring at 80°C overnight. The reaction mixture was left to be cooled to room temperature and then concentrated under reduced pressure. To the residue were added EtOH (200 mL) and water (200 mL), followed by stirring. The precipitate was collected by filtration. To the obtained precipitate was added chloroform, followed by dissolving therein, and $MgSO_4$, activated carbon (10 g), and basic silica gel (100 mL) were added thereto, followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain ethyl 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine-4-carboxylate (23.3 g).

[0099]

Preparation Example 7

To a mixture of ethyl 6-cyclohexyl-2-methylthieno[2,3-d]pyrimidine-4-carboxylate (29.3 g), calcium chloride (18 g), and THF (200 mL) was added $NaBH_4$ (5.5 g) in small divided portions at room temperature, and then EtOH (200 mL) was slowly added thereto over 5 minutes, followed by stirring at room temperature for 4 hours. To the reaction mixture was added ice water, followed by stirring, adding 1 M hydrochloric acid until the suspension becomes a solution state, and then extracting with EtOAc. The organic layer was washed sequentially with water, saturated aqueous sodium bicarbonate, and brine. To the organic layer were added $MgSO_4$, activated carbon, and basic silica gel,

followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/EtOAc) to obtain (6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methanol (12.7 g).

[0100]

Preparation Example 7-1

To a mixture of ethyl 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine-4-carboxylate (13.0 g), THF (150 mL), and EtOH (150 mL) was added calcium chloride (6.6 g), followed by stirring at room temperature for 30 minutes and then adding $NaBH_4$ (1.8 g) in small divided portions over 15 minutes under ice-cooling. After stirring at room temperature for 4.5 hours, to the reaction mixture were added water (100 mL) and EtOAc (100 mL) under ice-cooling. 1 M Hydrochloric acid (100 mL) was added thereto until the suspension became a solution, followed by concentration under reduced pressure and extracting with EtOAc. The organic layer was washed sequentially with water, saturated aqueous sodium bicarbonate, and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/EtOAc) to obtain [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methanol (9.35 g).

[0101]

Preparation Example 8

To a mixture of [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methanol (16.0 g), TEA (10 mL) and DCM (200 mL) was added dropwise MsCl (5.0 mL) at 0°C for 15 minutes, followed by stirring at the same temperature for 1 hour. To the reaction mixture was added saturated aqueous sodium bicarbonate, followed by extraction with chloroform. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate and brine. To the organic layer were added $MgSO_4$, activated carbon (5 g), and basic silica gel (20 mL), followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl methanesulfonate (18.9 g).

[0102]

Preparation Example 8-7

To a mixture of [2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-yl]methanol (6.42 g) and EtOAc (65 mL) were added dropwise TEA (4.5 mL) and MsCl (2.1 mL) under ice-cooling, followed by stirring at 0°C for 1 hour. The reaction mixture was filtered and then to the liquid was added saturated aqueous sodium bicarbonate, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure to obtain [2-(4,4-

dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-yl]methyl methanesulfonate (9.3 g).

[0103]

Preparation Example 9

To a mixture of N-(4,6-dichloro-2-methylpyrimidin-5-yl)-4,4-dimethylcyclocarboxamide (23.8 g) and EtOH (200 mL) were added thiourea (6 g) and formic acid (900 μL), followed by heating and stirring at 85°C for 15 hours. To the reaction mixture was added water, followed by extraction with chloroform. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/MeOH) to obtain 2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-ol (16.2 g).

[0104]

Preparation Example 10

Under an argon atmosphere, to a suspension of zinc powder (7.5 g) in THF (50 mL) were added dibromoethane (200 μL) and trimethylsilylchloride (200 μL), and then a solution of iodomethyl benzoate (15 g) in THF (50 mL) was added thereto, followed by stirring at room temperature for 1 hour. Then, a solution of 7-chloro-2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidine (10.9 g) in THF (50 mL) and $Pd(PPh_3)_4$ (4.25 g) were added thereto, followed by stirring at room temperature for 15 hours. The reaction mixture was filtered through Celite and then concentrated under reduced pressure. To the residue was added a 1 M aqueous NH_4Cl solution, followed by extraction with EtOAc. To the organic layer were added $MgSO_4$ and basic silica gel, followed by stirring, filtrating, and then concentrating under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc) to obtain [2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-yl]methyl benzoate (13.8 g).

[0105]

Preparation Example 11

To a mixture of [2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-yl]methyl benzoate (13.8 g) and MeOH (250 mL) was added a 28% $NaOCH_3$ solution (670 μL) in MeOH, followed by stirring at room temperature for 3 hours. The reaction mixture was neutralized by the addition of 4 M HCl/EtOAc (870 μL), and concentrated under reduced pressure. To the residue was added water, followed by extraction with EtOAc. To the organic layer were added $MgSO_4$ and basic silica gel, followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc) to obtain [2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-yl]methanol (7.9 g).

[0106]

Preparation Example 12

To a mixture of 2-amino-5-cyclohexylthiophene-3-carboxamide (53.5 g) and THF (500 mL) were added dropwise acetyl chloride (18 mL) and TEA (36 mL) under ice-cooling, followed by stirring at room temperature for 17 hours. The reaction mixture was concentrated under reduced pressure. To the residue were added EtOH (500 mL) and a 1 M aqueous NaOH solution (500 mL), followed by stirring at 80°C for 24 hours. The reaction mixture was left to be cooled to room temperature, and 1 M hydrochloric acid (500 mL) was added thereto, followed by stirring. The precipitate was collected by filtration, washed with water, and dried by blowing air to obtain 6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4(3H)-one (57.0 g).

[0107]

Preparation Example 13

To a mixture of (6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methanol (1.28 g) and DCM (20 mL) were added thionyl chloride (1 mL) and DMF (50 μL), followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, azeotroped with toluene, and dried. To the residue was added EtOAc. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/EtOAc) to obtain 4-(chloromethyl)-6-cyclohexyl-2-methylthieno[2,3-d]pyrimidine (663 mg).

[0108]

Preparation Example 14

To a mixture of 4-chloro-6-cyclohexyl-2-methylthieno[2,3-d]pyrimidine (1.0 g) and DMF (40 mL) were added (E)-1-ethoxyethene-2-boronic acid pinacol ester (900 mg) and K_3PO_4 (4.3 g), and $Pd(PPh_3)_4$ (500 mg) was added thereto under an argon atmosphere, followed by heating and stirring at 85°C for 2 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, then concentrated under reduced pressure, and purified by silica gel column (hexane/EtOAc) to obtain 6-cyclohexyl-4-[(E)-2-ethoxyvinyl]-2-methylthieno[2,3-d]pyrimidine (885 mg).

[0109]

Preparation Example 15

To tert-butyl 4-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-3,3-dimethylpiperazine-1-carboxylate (645 mg) and dioxane (6.45 mL) was added 4 M HCl/EtOAc (1.66 mL), followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. To the residue was added EtOAc, followed by stirring. The precipitate was filtered and dried under reduced

pressure to obtain 6-(4,4-dimethylcyclohexyl)-4-[(2,2-dimethylpiperazin-1-yl)methyl]-2-methylthieno[2,3-d]pyrimidine (422 mg).

[0110]

Preparation Example 15-1

To tert-butyl (1S,4S)-5-{[2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-yl]methyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (476 mg) and DCM (10 mL) was added trifluoroacetic acid (2.0 mL), followed by stirring at room temperature for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column to obtain 7-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidine (332 mg).

[0111]

Preparation Example 16

To a mixture of 6-cyclohexyl-4-[(E)-2-ethoxyvinyl]-2-methylthieno[2,3-d]pyrimidine (300 mg) and THF (3 mL) was added 1 M hydrochloric acid (3 mL), followed by stirring at room temperature for 30 minutes. To the reaction mixture was added saturated aqueous sodium bicarbonate to adjust the pH to 8 to 9, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/MeOH) to obtain (Z)-2-(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)ethenol (248 mg).

[0112]

Preparation Example 17

To a mixture of (Z)-2-(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)ethenol (430 mg) and MeOH (10 mL) was added $NaBH_4$ (65 mg) in small divided portions, followed by stirring for 15 minutes. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed sequentially with a saturated aqueous NH_4Cl solution and brine, and dried over Na_2SO_4, and the residue was purified by silica gel column (hexane/EtOAc) to obtain 2-(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)ethanol (315 mg).

[0113]

Preparation Example 18

To a mixture of ethyl 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine-4-carboxylate (1.0 g) and EtOH (10 mL) was added a 1 M aqueous NaOH solution (3.9 mL) under ice-cooling, followed by stirring at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and 1 M hydrochloric acid was added thereto, followed by stirring for 30 minutes. The precipitate

was collected by filtration, washed with water and then with hexane, dried by flowing air, and then dried under reduced pressure to obtain 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine-4-carboxylic acid (900 mg).

[0114]

Preparation Example 19

To a mixture of [2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-yl]methanol (500 mg) and DCM (10 mL) was added Dess-Martin periodinane (1.46 g) under ice-cooling, followed by stirring at 0°C for 3 hours. To the reaction mixture was added an aqueous $Na_2S_2O_3$ solution, followed by extraction with DCM. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over Na_2SO_4, and then concentrated under reduced pressure to obtain 2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidine-7-carbaldehyde (492 mg). To a mixture of the obtained aldehyde, NaH_2PO_4 (245 mg), 2-methyl-2-butene (542 μL), water (5 mL), and acetone (10 mL) was added $NaClO_2$ (231 mg) under ice-cooling, followed by stirring at room temperature for 1 hour. To the reaction mixture were added an aqueous $Na_2S_2O_3$ solution and Na_2SO_4, followed by extraction with a mixed solution (1:9) of 2-propanol and chloroform. The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure to obtain 2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidine-7-carboxylic acid (870 mg).

[0115]

Preparation Example 20

To a mixture of 4-chloro-6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine (1.0 g), tributyl(1-ethoxyvinyl)stannane (1.16 mL), and toluene (10.8 mL) was added $Pd(PPh_3)_4$ (392 mg), followed by heating to reflux for 5 hours. The reaction mixture was left to be cooled to room temperature, and to the reaction mixture were added a saturated aqueous NH_4Cl solution, followed by extraction with EtOAc. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure to obtain a crude product (1.12 g) containing 6-(4,4-dimethylcyclohexyl)-4-(1-ethoxyvinyl)-2-methylthieno[2,3-d]pyrimidine. To this crude product were added EtOH (9.0 mL) and 1 M hydrochloric acid (10.2 mL) at room temperature, followed by stirring at 50°C overnight. The reaction mixture was left to be cooled and concentrated under reduced pressure. To the residue was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column to obtain 1-[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]ethanone (820 mg).

[0116]

Preparation Example 22

A mixed solution of MeOH (2 mL) and THF (15 mL) was cooled in an ice bath, and NaH (60% oil, 600 mg) was added thereto, followed by stirring for 15 minutes. Then, a solution of 6-bromo-4-chloro-2-methylthieno[2,3-d]pyrimidine (2.0 g) in THF (5 mL) was added thereto, followed by stirring at room temperature for 2 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc) to obtain 6-bromo-4-methoxy-2-methylthieno[2,3-d]pyrimidine (1.8 g).

[0117]

Preparation Example 23

To a mixture of 2-methylthieno[2,3-d]pyrimidin-4(3H)-one (5.0 g) and AcOH (50 mL) was added NCS (4.8 g), followed by heating and stirring at 40°C for 2 days. The reaction mixture was concentrated under reduced pressure. To the residue was added water, followed by stirring, and the precipitate was collected by filtration and then dried to obtain 6-chloro-2-methylthieno[2,3-d]pyrimidin-4(3H)-one (5.5 g).

[0118]

Preparation Example 24

To a mixture of 4-chloro-6-cyclohexyl-2-methylthieno[2,3-d]pyrimidine (27.3 g), DABCO(1.2 g) and DMSO (150 mL) was slowly added an aqueous solution (14 mL) of KCN (8 g), followed by stirring at room temperature for 15 hours. To the reaction mixture was added water (150 mL) under ice-cooling, followed by stirring. The precipitate was collected by filtration and dissolved in chloroform. To the organic layer were added $MgSO_4$, activated carbon (2 g), and basic silica gel (100 mL), followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain 6-cyclohexyl-2-methylthieno[2,3-d]pyrimidine-4-carbonitrile (23.7 g).

[0119]

Preparation Example 25

Under an argon atmosphere, to DME (12.5 mL) that had been ice-cooled was added NaH (60% oil, 203 mg), followed by stirring for 10 minutes. To this mixture was added dropwise a solution of ethyl 3-(1,1-dioxidothiomorpholin-4-yl)-3-oxopropanoate (1.40 g) in DME (10 mL), followed by stirring at the same temperature for 30 minutes. Then, 4-chloro-6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine (750 mg) was added thereto, followed by stirring at 60°C overnight. The reaction mixture was left to be cooled, and then a saturated aqueous NH_4Cl solution was added thereto, followed by extraction with EtOAc. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column to obtain ethyl 2-[6-(4,4-dimethylcyclohexyl)-2-

methylthieno[2,3-d]pyrimidin-4-yl]-3-(1,1-dioxidothiomorpholin-4-yl)-3-oxopropanoate (559 mg).

[0120]

Preparation Example 28

To a mixture of 6-bromo-4-[(1,1-dioxidothiomorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine (200 mg), 4,4,5,5-tetramethyl-2-(spiro[2.5]octa-5-en-6-yl)-1,3,2-dioxaborolane (185 mg), and dioxane (4 mL) were added Pd_2dba_3 (25 mg), dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl)phosphine (50 mg), K_3PO_4(340 mg), and water (200 μL), followed by heating and stirring at 100°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by a basic silica gel column (hexane/EtOAc) to obtain 4-[(1,1-dioxidothiomorpholin-4-yl)methyl]-2-methyl-6-(spiro[2.5]octa-5-en-6-yl)thieno[2,3-d]pyrimidine (167 mg).

[0121]

Preparation Example 31

To a mixture of N-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]cycloheptaneamine (132 mg) and CH_3CN (3 mL) were added CH_3I (100 μL) and DIPEA (200 μL), followed by stirring at room temperature for 15 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc) to obtain N-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]-N-methylcycloheptaneamine (77 mg).

[0122]

Preparation Example 32

To a mixture of N-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}cyclopentaneamine (128 mg) and DMF (3 mL) were added 3-bromopropan-1-ol (100 μL) and Na_2CO_3 (110 mg), followed by stirring at 100°C for 15 hours. The reaction mixture was cooled to room temperature and then water was added thereto, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc) to obtain 3-(cyclopentyl{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}amino)propan-1-ol (88 mg).

[0123]

Preparation Example 33

To a mixture of (6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl methanesulfonate (500 mg) and CH_3CN (10 mL) was added cyclopentylamine (1.0 mL), followed by stirring at room temperature for 3 hours. To the reaction mixture was added

water, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc) and silica gel column (hexane/EtOAc) to obtain N-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]cyclopentaneamine (326 mg).

[0124]

Preparation Example 34

To a mixture of (6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl methanesulfonate (150 mg), cyclopentylmethylamine (100 mg), and CH_3CN (3 mL) was added DIPEA (200 μL), followed by stirring at room temperature overnight. To the reaction mixture was added saturated aqueous sodium bicarbonate, followed by extraction with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure, and the residue was purified by silica gel column (hexane/EtOAc) to obtain N-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]-N-methylcyclopentaneamine (131 mg).

[0125]

Preparation Example 37

To a mixture of (4,4-dimethylcyclohexyl)acetaldehyde (27.3 g) and DMF (100 mL) were added 2-cyanoacetamide (12 g), sulfur (5 g), and TEA (24 mL), followed by heating and stirring at 60°C for 12 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed sequentially with water and brine, and then Na_2SO_4 and activated carbon (2 g) were added thereto, followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain 2-amino-5-(4,4-dimethylcyclohexyl)thiophene-3-carboxamide (33.0 g).

[0126]

Preparation Example 38

To a mixture of 2-amino-5-(4,4-dimethylcyclohexyl)thiophene-3-carboxamide (33 g), pyridine (40 mL), and DCM (200 mL) was added dropwise acetyl chloride (14 mL) at 0°C, followed by stirring at room temperature for 1.5 hours. The reaction mixture was concentrated under reduced pressure, and then water and 1 M hydrochloric acid were added thereto, followed by extraction with chloroform. The organic layer was washed sequentially with water, saturated aqueous sodium bicarbonate, and brine. To the organic layer were added $MgSO_4$, activated carbon (2 g), and basic silica gel (100 mL), followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain 2-acetamide-5-(4,4-dimethylcyclohexyl)thiophene-3-carboxamide (37.3 g).

[0127]

Preparation Example 39

To a mixture of WSC hydrochloride (4.5 g), HOBt (3.2 g), and DMF (50 mL) were added difluoroacetic acid (2 mL) and 2-amino-5-cyclohexylthiophene-3-carboxamide (5.0 g), followed by stirring at room temperature for 3 days. To the reaction mixture was added 50% brine, followed by extraction with EtOAc. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate, water, and brine. To the organic layer were added $MgSO_4$, and basic silica gel was added thereto, followed by stirring. The mixture was filtered through Celite and then concentrated under reduced pressure to obtain 5-cyclohexyl-2-[(difluoroacetyl)amino]thiophene-3-carboxamide (7.0 g).

[0128]

Preparation Example 40

To a mixture of 4,4-dimethylcyclohexane carboxylic acid (20.4 g) and toluene (150 mL) was added thionyl chloride (19 mL), followed by stirring at 80°C for 15 hours. The reaction liquid was concentrated under reduced pressure. To the residue was added 4,6-dichloro-2-methylpyrimidine-5-amine (23.3 g), followed by stirring at 90°C for 10 minutes. DCE (207 mL) was added thereto, followed by stirring at 100°C for 15 hours. The reaction mixture was cooled to room temperature, and then water was added thereto, followed by extraction with chloroform. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc) to obtain N-(4,6-dichloro-2-methylpyrimidin-5-yl)-4,4-dimethylcyclohexanecarboxamide (23.8 g).

[0129]

Preparation Example 41

To a mixture of adamanthane-1-carboxylic acid (2.43 g) and DCM (40 mL) was added 1-chloro-N,N,2-trimethylpropenylamine (2.23 mL) at room temperature, followed by stirring for 1 hour. To this mixture were added 4,6-dichloro-2-methylpyrimidine-5-amine (2.0 g) and pyridine (2.71 mL), followed by stirring at room temperature for additional 1 hour. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column to obtain N-(4,6-dichloro-2-methylpyrimidin-5-yl)adamanthane-1-carboxamide (3.51 g).

[0130]

Preparation Example 42

To a mixture of thiomorpholine-1,1-dioxide (3.22 g) and DCM (48 mL) was added ethyl 3-chloro-3-oxopropanoate (2.0 mL) under ice-cooling, followed by stirring at the same temperature for 30 minutes. To the reaction mixture was added water, followed by extraction with chloroform. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure to obtain a crude product (3.11 g) of ethyl 3-

(1,1-dioxidothiomorpholin-4-yl)-3-oxopropanoate. The crude product was used as it was for the next reaction without purification.

[0131]

Preparation Example 43

Under an argon atmosphere, to a mixture of 2-(4,4-dimethylcyclohexyl)ethanol (25.3 g) and DCM (200 mL) were added DMSO (50 mL) and TEA (100 mL), and a sulfur trioxide-pyridine complex (77.7 g) was added in small divided portions while maintaining the inner temperature to 10°C or lower under ice-cooling. After stirring at room temperature for 2 hours, to the reaction mixture was added ice water, followed by concentration under reduced pressure and then extraction with chloroform. The organic layer was washed sequentially with 1 M hydrochloric acid and brine. To the organic layer was added $MgSO_4$, followed by stirring. Then, the mixture was filtered and concentrated under reduced pressure to obtain (4,4-dimethylcyclohexyl)acetaldehyde (27.3 g).

[0132]

Preparation Example 44

To a mixture of ethyl 1-(3-ethoxy-3-oxopropanoyl)piperidin-4-yl malonate (1.02 g) and EtOH (5.1 mL) was added NaOEt (20% EtOH solution, 105 mg), followed by stirring at room temperature for 30 minutes. To the reaction mixture was added a saturated aqueous NH_4Cl solution, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column to obtain ethyl 3-(4-hydroxypiperidin-1-yl)-3-oxopropanpate (368 mg).

[0133]

Preparation Example 45

To a mixture of a 30% hydrogen peroxide solution (2.7 mL) and DCM (100 mL) was added dropwise trifluoroacetate anhydride (4.4 mL) under ice-cooling, and a solution of 1-benzyl-5-methyl-1,2,3,6-tetrahydropyridine (2.1 g) in DCM (5 mL) was added thereto, followed by stirring for 1.5 hours. To the reaction mixture was added a saturated aqueous Na_2SO_3 solution, followed by extraction with DCM. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/MeOH) to obtain trans-1-benzyl-3-methylpiperidine-3,4-diol (2.0 g).

[0134]

Preparation Example 46

To a solution of 5-benzyl-2,5-diazabicyclo[2.2.2]octan-3-one (400 mg) in EtOH (5 mL) was added 20% $Pd(OH)_2/C$ (65 mg), followed by stirring at room temperature overnight at normal pressure under a hydrogen atmosphere. The reaction mixture was

filtered through Celite and then concentrated under reduced pressure to obtain 2,5-diazabicyclo[2.2.2]octan-3-one (219 mg).

[0135]

Preparation Example 47

A mixture of a trans-1-benzyl-4-methylpiperidine-3,4-diolacetate (256 mg), 10% Pd/C (193 mg), acetic acid (5 mL), and EtOH (5 mL) was stirred at room temperature for 12 hours under a hydrogen atmosphere of 3 atm. The reaction mixture was filtered through Celite and then concentrated under reduced pressure to obtain trans-4-methylpiperidine-3,4-diol acetate (212 mg), which was used for the next reaction without purification.

[0136]

Preparation Example 48

Under a hydrogen atmosphere of 3 atm, a mixture of trans-1-benzyl-3-methylpiperidine-3,4-diol (460 mg), DIBOC (907 mg), 20% $Pd(OH)_2/C$ (291 mg), and EtOAc (28 mL) was stirred at room temperature for 12 hours. The reaction mixture was filtered through Celite and then concentrated under reduced pressure to obtain tert-butyl trans-3,4-dihydroxy-3-methylpiperidine-1-carboxylate (80 mg).

[0137]

Preparation Example 49

To a mixture of 10% Pd/C (409 mg) and MeOH (7 mL) was added a mixture of ammonium formate (2.92 g) and 1-(diphenylmethyl)-2,2-dimethylazetidin-3-ol (1.03 g) in MeOH (7 mL) and THF (14 mL), followed by stirring at 50°C for 2 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was purified by basic silica gel column (chloroform/MeOH) to obtain 2,2-dimethylazetidin-3-ol (378 mg).

[0138]

Preparation Example 50

To a mixture of a 30% hydrogen peroxide solution (3.6 mL) and DCM (120 mL) were added trifluoroacetic anhydride (6.0 mL) at 0°C, and a solution of 1-benzyl-4-methyl-1,2,3,6-tetrahydropyridine (2.9 g) in DCM (10 mL) was further added thereto, followed by stirring at room temperature for 12 hours and then stirring at 50°C for additional 3 hours. To the reaction mixture was added an aqueous Na_2SO_3 solution, followed by stirring until peroxides disappeared, and then extracting with DCM. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/MeOH) to obtain 3-benzyl-6-methyl-7-oxa-3-azabicyclo[4.1.0]heptane (1.8 g).

[0139]

Preparation Example 51

To a mixture of 3-benzyl-6-methyl-7-oxa-3-azabicyclo[4.1.0]heptane (700 mg) in THF (10 mL) was added AcOH (10 mL), followed by stirring at 80°C for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/MeOH) to obtain trans-1-benzyl-4-methylpiperidine-3,4-diolacetate (256 mg).

[0140]

Preparation Example 52

To a mixture of tert-butyl trans-3,4-dihydroxy-3-methylpiperidine-1-carboxylate (80 mg) and EtOAc (5 mL) was added 4 M HCl/EtOAc (0.4 mL) at room temperature, followed by stirring for 12 hours. The reaction mixture was concentrated under reduced pressure to obtain trans-3-methylpiperidine-3,4-diol hydrochloride (50 mg).

[0141]

Example 1

To a mixture of thiomorpholine-1,1-dioxide (65 mg) and DMF (4 mL) were added (6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl methanesulfonate (110 mg) and TEA (150 μL), followed by stirring at room temperature for 24 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc) to obtain 6-cyclohexyl-4-[(1,1-dioxidothiomorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine (94 mg).

[0142]

Example 2

To a mixture of thiomorpholine-1,1-dioxide (70 mg) and DMF (4 mL) were added [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl methanesulfonate (120 mg) and TEA (150 μL), followed by stirring at room temperature overnight. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc) to obtain 6-(4,4-dimethylcyclohexyl)-4-[(1,1-dioxidothiomorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine (102 mg).

[0143]

Example 31, Example 31-1

A racemic compound of trans-1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidine-3,4-diol (321 mg) was purified by supercritical fluid chromatography (column: manufactured by Daicel Corporation, Chiralpak IC 10 × 250 mm, mobile phase: liquid carbon dioxide gas/0.1% diethylamine-containing MeOH =

75/25, flow rate of 10 mL/min, column temperature: 40°C). To the residue was added IPE, followed by stirring, and then the precipitate was collected by filtration to obtain optically active trans-1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidine-3,4-diol (110 mg) having a retention time of 8.48 minutes and optically active trans-1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidine-3,4-diol (112 mg) having a retention time of 9.44 minutes, respectively.

[0144]

Example 33

To a mixture of 6-cyclohexyl-4-[(2,2-dimethylmorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine (130 mg) and EtOAc (2 mL) was added 4 M HCl/EtOAc (100 μL), followed by stirring at room temperature. The precipitated solid was collected by filtration to obtain 6-cyclohexyl-4-[(2,2-dimethylmorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine hydrochloride (90 mg).

[0145]

Example 52

To a mixture of [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl methanesulfonate (120 mg) and DMF (4 mL) were added piperidin-4-ol (70 mg) and TEA (100 μL), followed by stirring at room temperature for 18 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc). To the obtained purified product was added EtOAc, and then 4 M HCl/EtOAc (100 μL) was added thereto, followed by stirring at room temperature. The precipitate was collected by filtration to obtain 1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidin-4-ol hydrochloride (115 mg).

[0146]

Example 85

A suspension of [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl methanesulfonate (100 mg), cis-pyrrolidine-3,4-diol hydrochloride (57 mg), and K_2CO_3 (75 mg) in DMF (3 mL) was stirred at 50°C for 12 hours. The reaction mixture was cooled to room temperature, and water was added thereto, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/MeOH). The obtained purified product was suspended in IPE, and the precipitate was collected by filtration to obtain cis-1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}pyrrolidine-3,4-diol (9 mg).

[0147]

Example 96

A suspension of [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl methanesulfonate (100 mg), 2-(azetidin-3-yl)propan-2-ol hydrochloride (62 mg) and K_2CO_3 (94 mg) in DMF (1.0 mL) was stirred at 70°C for 12 hours. The reaction mixture was cooled to room temperature, and water was added thereto, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/MeOH) to form a salt with 4 M HCl/EtOAc, and then washed with EtOAc to obtain 2-(1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}azetidin-3-yl)propan-2-ol hydrochloride (32 mg).

[0148]

Example 105

To a mixture of 5-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]-2,5-diazabicyclo[2.2.2]octan-3-one (113 mg) and DMF was added NaH (60% oil, 12 mg) under ice-cooling, followed by stirring at the same temperature for 5 minutes, and CH_3I (38 μL) was added thereto, followed by stirring at the same temperature for 20 minutes. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc). The residue was dissolved in EtOAc, and an excess amount of 4 M HCl/EtOAc was added thereto, followed by concentration under reduced pressure. To the obtained purified product was added Et_2O, followed by stirring, and the precipitate was collected by filtration to obtain 5-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]-2-methyl-2,5-diazabicyclo[2.2.2]octan-3-one hydrochloride (83 mg).

[0149]

Example 106

To a mixture of (Z)-2-(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)ethenol (120 mg) and AcOH (12 mL) were added morpholine (400 μL) and $NaBH(OAc)_3$ (200 mg), followed by stirring at room temperature for 15 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate, followed by extraction with chloroform. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc) to obtain 6-cyclohexyl-2-methyl-4-[2-(morpholin-4-yl)ethyl]thieno[2,3-d]pyrimidine (53 mg).

[0150]

Example 107

To a mixture of 2-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]-2,5-diazabicyclo[2.2.2]octan-3-one (67 mg), 1H-benzotriazole-1-methanol (54 mg), and

DCE was added $NaBH(OAc)_3$ (115 mg) at room temperature, followed by stirring at the same temperature for 5 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc) and the obtained purified product was dissolved in EtOAc. An excess amount of 4 M HCl/EtOAc was added thereto, followed by concentration under reduced pressure. To the residue was added Et_2O, followed by stirring, and the precipitate was collected by filtration to obtain 2-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]-5-methyl-2,5-diazabicyclo[2.2.2]octan-3-one hydrochloride (57 mg).

[0151]

Example 108

A mixture of 4-[(1,1-dioxidothiomorpholin-4-yl)methyl]-2-methyl-6-(spiro[2.5]octa-5-en-6-yl)thieno[2,3-d]pyrimidine (165 mg), THF (5 mL), and EtOH (5 mL) was allowed to undergo a reaction using H-Cube (registered trademark, 10% Pd/C cartridge, Thalesnano) at 50 bar and 50°C under a H_2 atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatorgraphy (chloroform/MeOH) to obtain 4-[(1,1-dioxidothiomorpholin-4-yl)methyl]-2-methyl-6-(spiro[2.5]octa-6-yl)thieno[2,3-d]pyrimidine (59 mg).

[0152]

Example 109

To a mixture of {(3S)-4-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]morpholin-3-yl}methanol (132 mg) and DMF was added NaH (60% oil, 15 mg) under ice-cooling, followed by stirring at the same temperature for 5 minutes, and then CH_3I (17 μL) was added thereto, followed by stirring at the same temperature for 30 minutes. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, then dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc) to obtain 6-cyclohexyl-4-{[(3S)-3-(methoxymethyl)morpholin-4-yl]methyl}-2-methylthieno[2,3-d]pyrimidine (102 mg).

[0153]

Example 112

To a mixture of piperidin-2-one (100 mg), THF (4 mL), and DMF (1 mL) was added NaH (60% oil, 40 mg), followed by stirring at room temperature for 30 minutes, and then (6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl methanesulfonate (150 mg) was added thereto, followed by further stirring at room temperature for 1 hour. To the reaction mixture were added water and 1 M hydrochloric acid, followed by extraction with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then

concentrated under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc) to obtain 1-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]piperidin-2-one (13 mg).

[0154]

Example 116

To a mixture of (6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl methanesulfonate (130 mg) and CH_3CN (5 mL) were added 3-fluoropiperidinehydrochloride (107 mg) and TEA (200 μL), followed by stirring at room temperature for 15 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc). To the obtained purified product were added EtOH and fumaric acid (35 mg), followed by dissolving therein and concentrating under reduced pressure. To the residue was added EtOH:acetone (1:5), followed by heating and dissolving therein, and leaving to be cooled under stirring. The precipitate was collected by filtration to obtain 6-cyclohexyl-4-[(3-fluoropiperidin-1-yl)methyl]-2-methylthieno[2,3-d]pyrimidine fumarate (105 mg).

[0155]

Example 126

A mixture of [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl methanesulfonate (100 mg), 2-oxa-6-azaspiro[3.3]heptaneoxalate (67 mg), K_2CO_3 (94 mg), and DMF (1.0 mL) was stirred at 80°C for 12 hours. The reaction mixture was cooled to room temperature, and water was added thereto, followed by extraction with EtOAc. The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by silica gel column (chloroform/MeOH), and fumaric acid (10 mg) was added thereto to form a salt, followed by washing with EtOAc, thereby obtaining 6-(4,4-dimethylcyclohexyl)-2-methyl-4-(2-oxa-6-azaspiro[3.3]hept-6-ylmethyl)thieno[2,3-d]pyrimidinefumarate (23 mg).

[0156]

Example 130

To a mixture of 2-(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)ethyl methanesulfonate (64 mg) and CH_3CN (2 mL) was slowly added piperidine (800 μL), followed by stirring at room temperature for 3 days. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc). To a solution of the obtained purified product in chloroform (3 mL) was added 4 M HCl/EtOAc (150 μL), followed by concentration under reduced pressure. To the residue was added EtOAc, followed by

heating and washing, and the precipitate was collected by filtration to obtain 6-cyclohexyl-2-methyl-4-[2-(piperidin-1-yl)ethyl]thieno[2,3-d]pyrimidine dihydrochloride (61 mg).

[0157]

Example 134

To a mixture of (6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl methanesulfonate (150 mg) and CH_3CN (2 mL) was slowly added a solution of (2S)-pyrrolidin-2-ylmethanol (100 mg) in CH_3CN (1 mL), followed by stirring at room temperature for 15 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc). To the obtained purified product were added EtOH and fumaric acid (39 mg), followed by dissolving therein and concentrating under reduced pressure. To the residue was added EtOH/acetone (1:10), followed by heating and dissolving therein. After leaving to be cooled under stirring, the precipitate was collected by filtration to obtain {(2S)-1-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]pyrrolidin-2-yl}methanolfumarate (76 mg).

[0158]

Example 150

To a mixture of 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl methanesulfonate (150 mg), DIPEA (209 μL), and DMF (2.25 mL) was added 2,2-dimethylazetidin-3-ol (54 mg), followed by stirring at room temperature for 18 hours. To the reaction mixture were added water and EtOAc, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc). The obtained purified product was dissolved in EtOAc (1.5 mL), and then a mixture of fumaric acid (38 mg) and MeOH (300 μL) was added thereto. The precipitate was collected by filtration to obtain 1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-2,2-dimethylazetidin-3-ol fumarate (106 mg).

[0159]

Example 152

To a mixture of 2-{[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]amino}-2-methylpropan-1-ol (55 mg) and DCM was added CDI(40 mg), followed by stirring at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column (hexane/EtOAc) to obtain 3-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]-4,4-dimethyl-1,3-oxazolidin-2-one (54 mg).

[0160]

Example 153

To a mixture of 6-(4,4-dimethylcyclohexyl)-4-[(2,2-dimethylpiperazin-1-yl)methyl]-2-methylthieno[2,3-d]pyrimidine (40 mg), pyridine (83 μL), and DCM (1.2 mL) was added acetic anhydride (49 μL), followed by stirring at room temperature for 30 minutes. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column. To a solution of the obtained purified product in EtOAc was added dropwise 4 M HCl/dioxane, and the precipitate was collected by filtration and dried to obtain 1-(4-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-3,3-dimethylpiperazin-1-yl)ethanone hydrochloride (35 mg).

[0161]

Example 155

To a mixture of 6-(4,4-dimethylcyclohexyl)-4-[(2,2-dimethylpiperazin-1-yl)methyl]-2-methylthieno[2,3-d]pyrimidine (222 mg), glycolic acid (52 mg), and NMP (3.2 mL) were added HATU (306 mg) and DIPEA (492 μL), followed by stirring at room temperature overnight. To the reaction mixture was added a saturated aqueous NH_4Cl solution, followed by extraction with EtOAc. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column to obtain 1-(4-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-3,3-dimethylpiperazin-1-yl)-2-hydroxyethanone (102 mg).

[0162]

Example 161

(3S)-1-{[2-(4,4-Dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-yl]methyl}pyrrolidin-3-ol (73 mg) was dissolved in EtOH (3 mL), and fumaric acid (24 mg) was added thereto, followed by concentration under reduced pressure. To the residue was added IPE, followed by stirring at room temperature. The precipitate was collected by filtration to obtain (3S)-1-{[2-(4,4-dimethylcyclohexyl)-5-methyl[1,3]thiazolo[5,4-d]pyrimidin-7-yl]methyl}pyrrolidin-3-ol fumarate (81 mg).

[0163]

Example 163

To a mixture of 5-benzyl-2-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]-2,5-diazabicyclo[2.2.2]octan-3-one (140 mg) and DCE (5 mL) was added 1-chloroethyl chloroformate (50 μL), followed by stirring at room temperature overnight. The reaction solution was purified by silica gel column (chloroform/MeOH/saturated aqueous NH_3) without concentration. The residue was dissolved in MeOH, and heated to reflux for 30 minutes. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column (chloroform/MeOH/saturated aqueous NH_3)

to obtain 2-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]-2,5-diazabicyclo[2.2.2]octan-3-one (87 mg).

[0164]

Example 187

To a mixture of N-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]cyclohexaneamine (47 mg) and DCM (4 mL) were added dropwise acetyl chloride (20 μL) and TEA (40 μL) at 0°C, followed by stirring at room temperature for 2.5 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed sequentially with 1 M hydrochloric acid, saturated aqueous sodium bicarbonate, and brine, dried over $MgSO_4$, and then concentrated under reduced pressure to obtain N-cyclohexyl-N-[(6-cyclohexyl-2-methylthieno[2,3-d]pyrimidin-4-yl)methyl]acetamide (50 mg).

[0165]

Example 188

To a mixture of N-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}tetrahydro-2H-pyran-4-amine (60 mg), pyridine (129 μL), and DCM (1.8 mL) was added acetic anhydride (76 μL), followed by stirring at room temperature for 30 minutes. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by silica gel column to obtain N-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-N-(tetrahydro-2H-pyran-4-yl)acetamide (23 mg).

[0166]

Example 190

To a mixture of N-{[6-(4,4-difluorocyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-1-methoxy-2-methylpropan-2-amine (110 mg), 1H-benzotriazole-1-methanol (86 mg), and DCE was added $NaBH(OAc)_3$ (182 mg), followed by stirring at room temperature for 4 hours. To the reaction mixture was added water, followed by extraction with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by basic silica gel column (hexane/EtOAc) to obtain N-{[6-(4,4-difluorocyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-1-methoxy-N,2-dimethylpropan-2-amine (93 mg). This product was dissolved in MeOH, and fumaric acid (27 mg) was added thereto, followed by concentration under reduced pressure to obtain N-{[6-(4,4-difluorocyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-1-methoxy-N,2-dimethylpropan-2-aminefumarate (117 mg).

[0167]

Example 191

To a mixture of N-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride (100 mg), CH_3I(16 μL) and DMF (2.0 mL) was added K_2CO_3 (60 mg), followed by stirring at 50°C overnight. The reaction mixture was left to be cooled, and a saturated aqueous NH_4Cl solution was added thereto, followed by extraction with EtOAc. The organic layer was washed sequentially with water and brine, and dried over $MgSO_4$. The residue was purified by silica gel column. The obtained purified product was dissolved in EtOAc, and 4 M HCl/EtOAc (55 μL) was added dropwise thereto. The precipitate was collected by filtration and then dried to obtain N-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-N-methyltetrahydro-2H-thiopyran-4-amine 1,1-dioxidehydrochloride (69 mg).

[0168]

Example 196

To a mixture of N-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}tetrahydro-2H-pyran-4-amine (100 mg), 1,4-dioxane-2,5-diol (64 mg), DCE(2 mL), and MeOH (1 mL) was added $NaBH(OAc)_3$ (170 mg) under ice-cooling, followed by stirring at 0°C for 1 hour. To the reaction mixture were added water and EtOAc, followed by extraction with EtOAc. The organic layer was washed with brine, dried, and then concentrated under reduced pressure. The residue was purified by silica gel column to obtain 2-[{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}(tetrahydro-2H-pyran-4-yl)amino]ethanol (51 mg).

[0169]

Example 198

To a mixture of [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl methanesulfonate (200 mg), DIPEA (139 μL), and DMF (3.0 mL) was added tetrahydro-2H-thiopyran-4-amine-1,1-dioxide (97 mg), followed by stirring at room temperature for 4 hours. To the reaction mixture was added a saturated aqueous NH_4Cl solution, followed by extraction with EtOAc. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column and dissolved in EtOAc, and 4 M HCl/EtOAc (137 μL) was added dropwise. The precipitate was collected by filtration and then dried to obtain N-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride (165 mg).

[0170]

Example 205

To a suspension of N-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-4-methyltetrahydro-2H-thiopyran-4-amine (55 mg) and sodium tungstate (IV) dihydrate (9.0 mg) in MeOH (1.1 mL) were sequentially added dropwise 1

M hydrochloric acid (313 μL) and a 35% hydrogen peroxide solution (56 μL) under ice-cooling, followed by stirring at the same temperature for 10 minutes, and further stirring at room temperature for 6 hours. To the reaction mixture that had been ice-cooled was added an aqueous $Na_2S_2O_3$ solution, followed by stirring at room temperature for 30 minutes. Then, saturated aqueous sodium bicarbonate was added thereto, followed by extraction with chloroform. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column. The obtained purified product was dissolved in EtOAc, and 4 M HCl/dioxane was added dropwise thereto. The precipitate was collected by filtration and then dried under reduced pressure to obtain N-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-4-methyltetrahydro-2H-thiopyran-4-amine-1,1-dioxidehydrochloride (22 mg).

[0171]

Example 206

To a mixture of 6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidine-4-carboxylic acid (150 mg), 4-methylpiperidin-4-ol (68 mg), HATU(262 mg), and NMP (2.1 mL) was added DIPEA (244 μL), followed by stirring at room temperature overnight. To the reaction mixture was added a saturated aqueous NH_4Cl solution, followed by extraction with EtOAc. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column. The obtained purified product was suspended in IPE, collected by filtration, and then dried under reduced pressure to obtain [6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl](4-hydroxy-4-methylpiperidin-1-yl)methanone (120 mg).

[0172]

Example 229

To a mixture of ethyl 2-[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]-3-(1,1-dioxidothiomorpholin-4-yl)-3-oxopropanpate (520 mg) and THF (16 mL) were added MeOH (2.7 mL) and a 1 M aqueous NaOH solution (3.9 mL) at room temperature, followed by stirring at 60°C for 8 hours. The reaction mixture was left to be cooled, and then 1 M hydrochloric acid was added thereto, followed by concentration under reduced pressure. To the residue was added EtOAc, followed by extraction. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column to obtain 2-[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]-1-(1,1-dioxidethiomorpholin-4-yl)ethanone (322 mg).

[0173]

In the same manner as the methods of Preparation Examples or Examples above, the compounds of Preparation Examples and Examples in Tables below were prepared.

[0174]

[Table 5]

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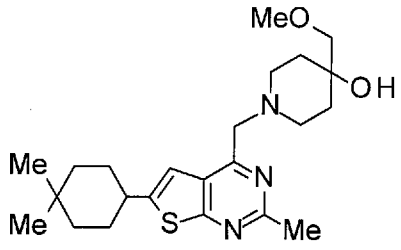
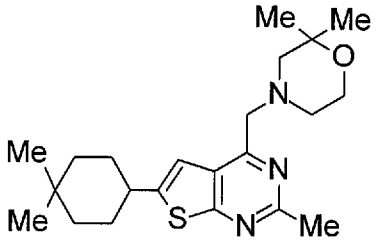
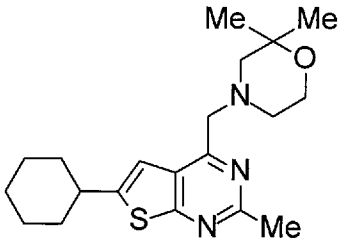
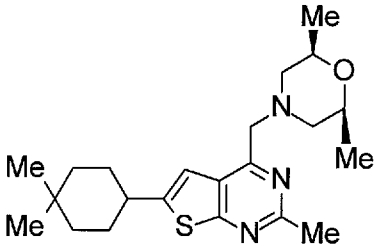
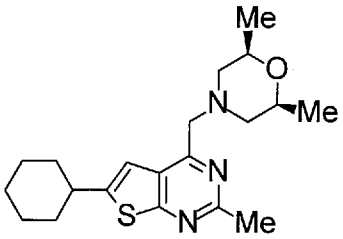
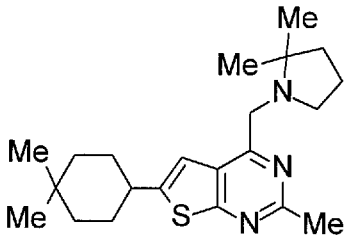
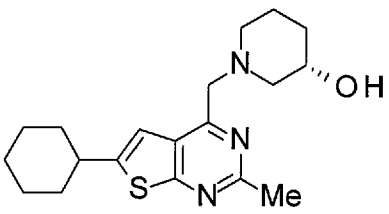
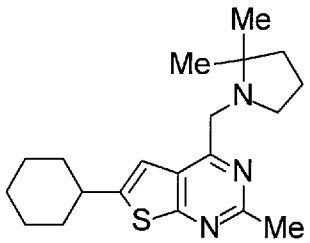
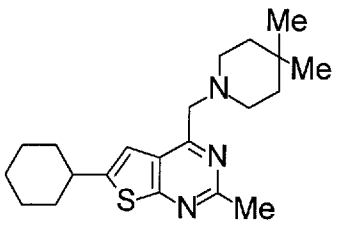
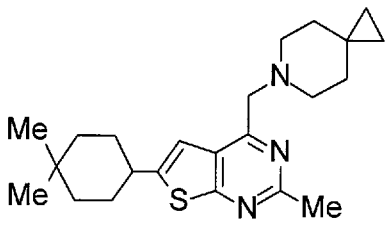
Pr1		Pr1-5	
Pr1-1		Pr1-6	
Pr1-2		Pr1-7	
Pr1-3 Chiral		Pr1-8	
Pr1-4		Pr1-9	

[0175]

[Table 6]

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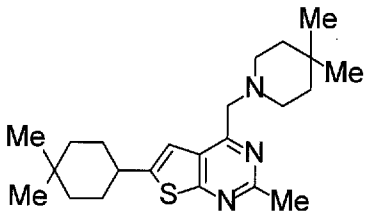
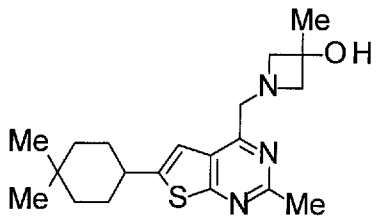
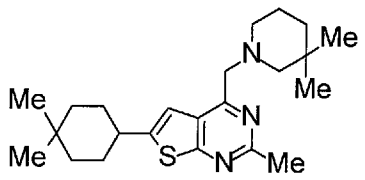
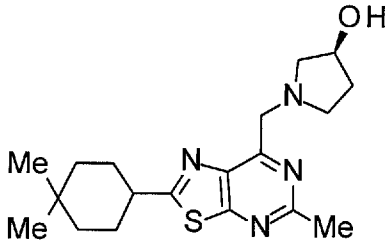
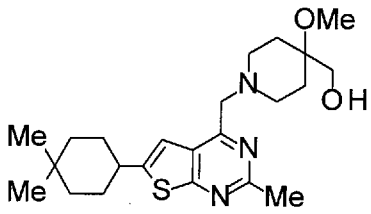
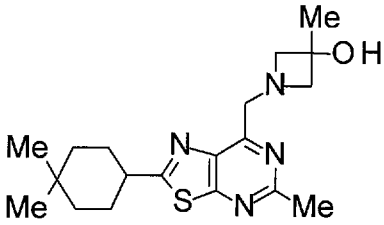
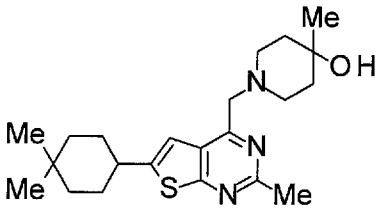
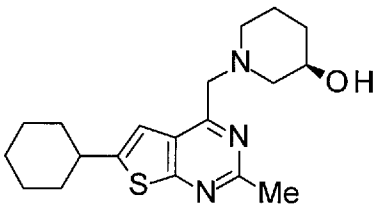
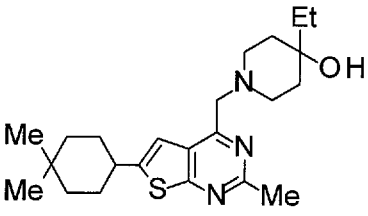
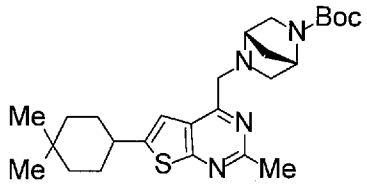
Pr1-10		Pr1-15	
Pr1-11		Pr1-16 Chiral	
Pr1-12		Pr1-17	
Pr1-13		Pr1-18 Chiral	
Pr1-14		Pr2	

[0176]

[Table 7]

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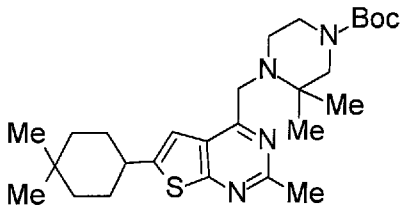
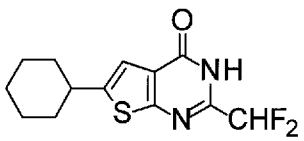
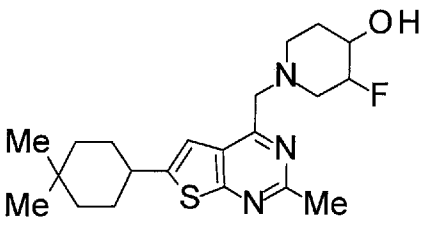
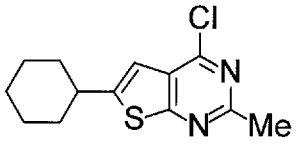
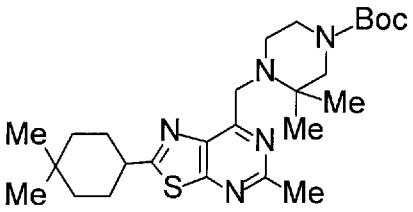
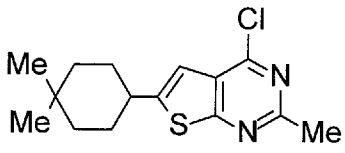
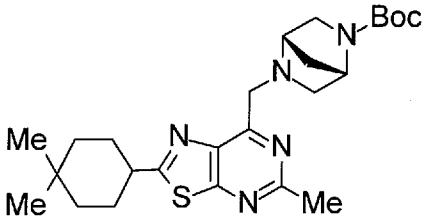
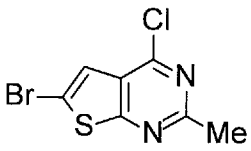
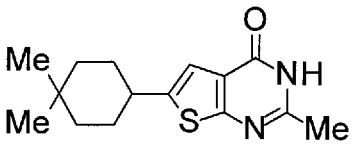
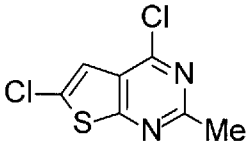
Pr2-1		Pr3-1	
Pr2-2		Pr4	
Pr2-3		Pr4-1	
Pr2-4 Chiral		Pr4-2	
Pr3		Pr4-3	

[0177]

[Table 8]

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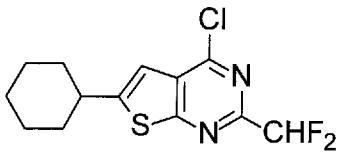
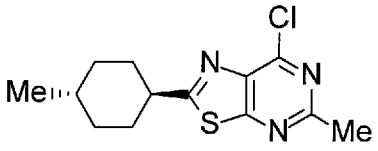
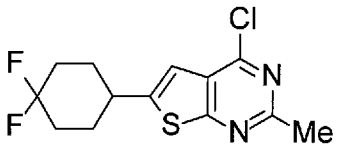
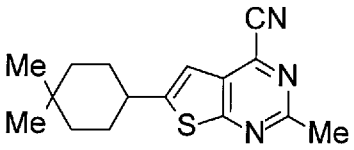
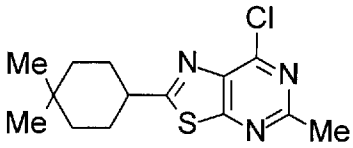
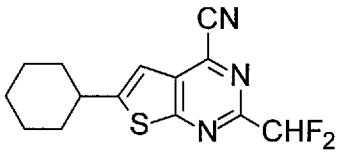
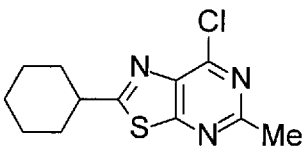
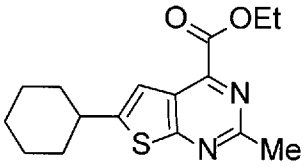
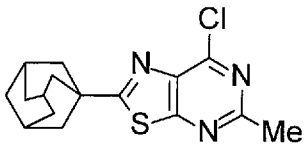
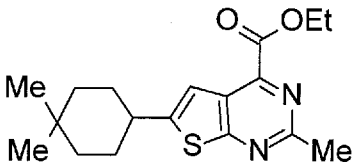
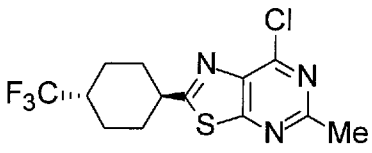
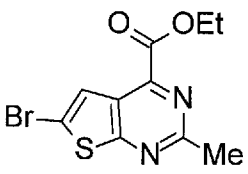
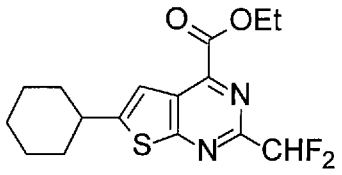
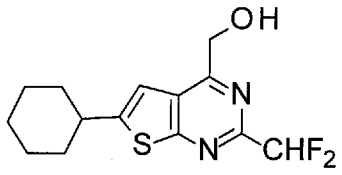
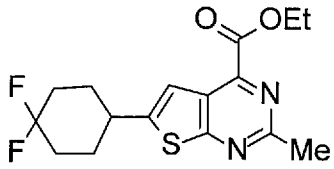
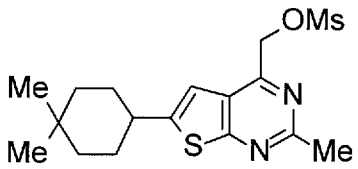
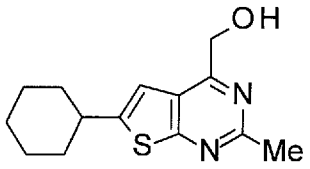
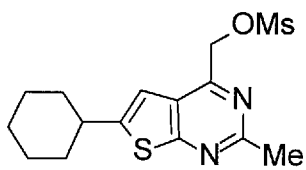
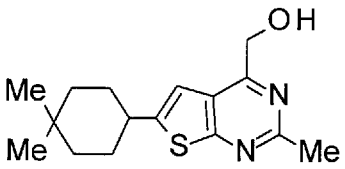
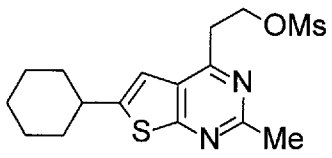
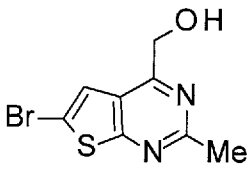
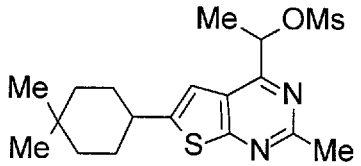
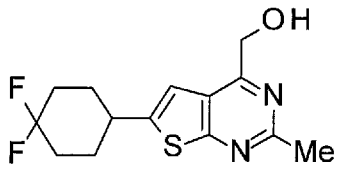
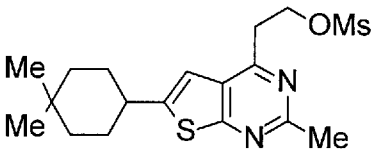
Pr4-4		Pr4-10	
Pr4-5		Pr5	
Pr4-6		Pr5-1	
Pr4-7		Pr6	
Pr4-8		Pr6-1	
Pr4-9		Pr6-2	

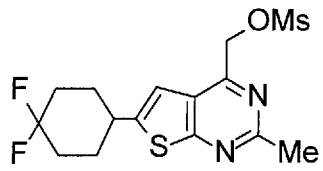
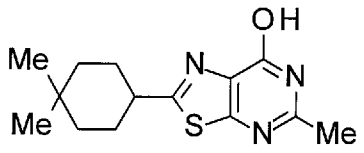
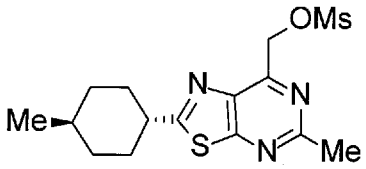
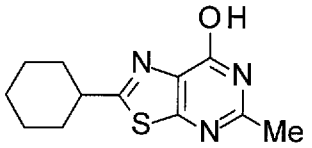
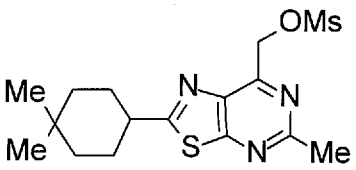
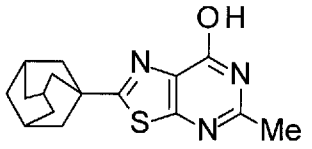
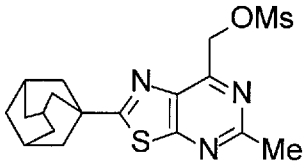
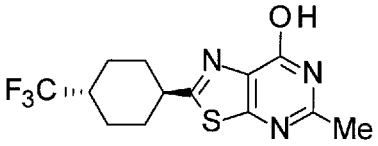
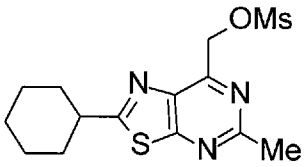
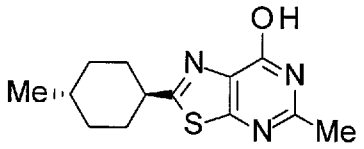
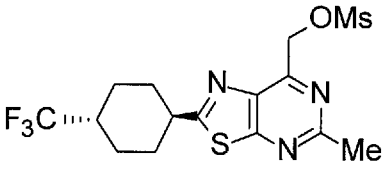
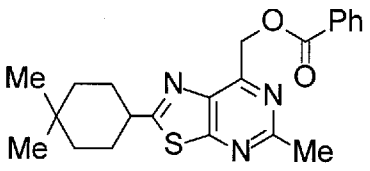
[0178]

[Table 9]

No. /Inf	Str	No	Str
Pr6-3		Pr7-4	
Pr6-4		Pr8	
Pr7		Pr8-1	
Pr7-1		Pr8-2	
Pr7-2		Pr8-3	
Pr7-3		Pr8-4	

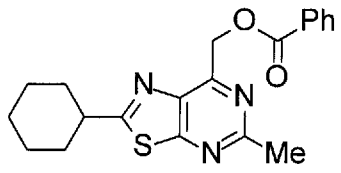
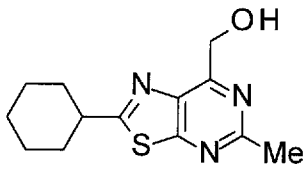
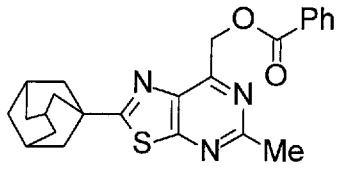
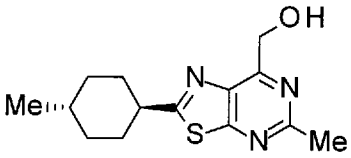
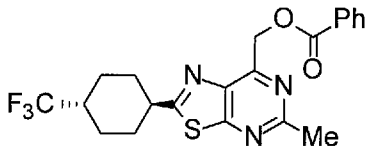
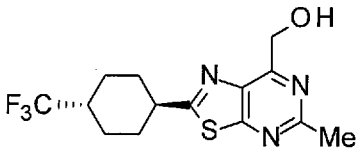
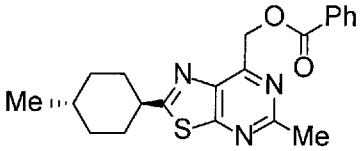
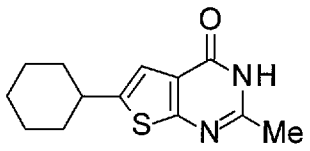
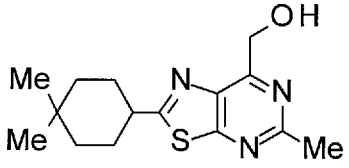
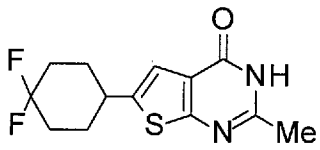
[0179]

[Table 10]

No. /Inf	Str	No. /Inf	Str
Pr8-5		Pr9	
Pr8-6		Pr9-1	
Pr8-7		Pr9-2	
Pr8-8		Pr9-3	
Pr8-9		Pr9-4	
Pr8-10		Pr10	

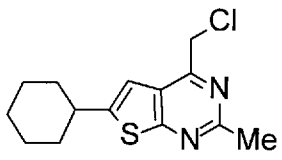
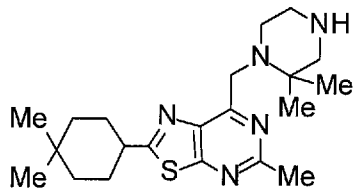
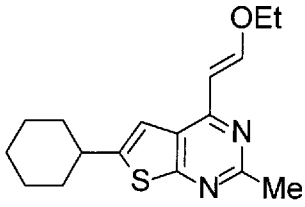
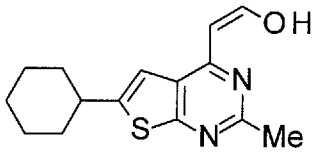
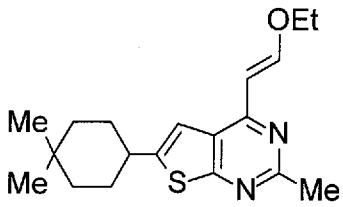
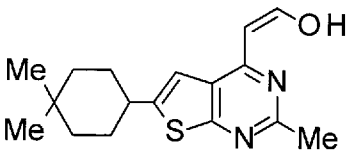
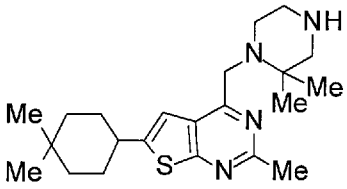
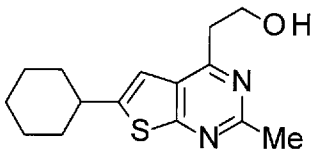
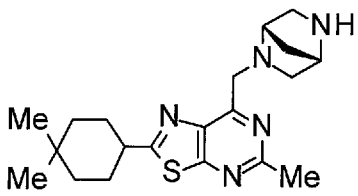
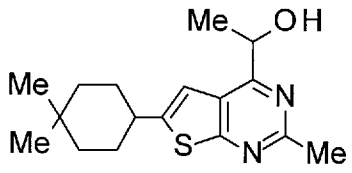
[0180]

[Table 11]

No. /Inf	Str	No. /Inf	Str
Pr10-1		Pr11-1	
Pr10-2		Pr11-2	
Pr10-3		Pr11-3	
Pr10-4		Pr12	
Pr11		Pr12-1	

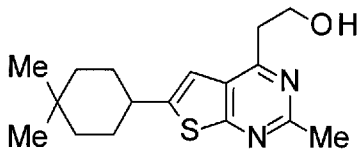
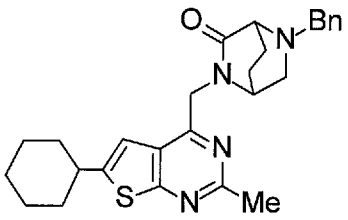
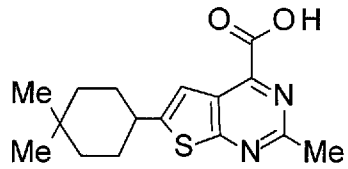
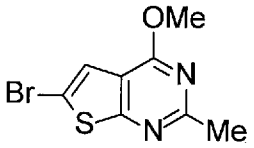
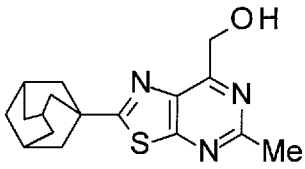
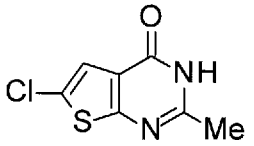
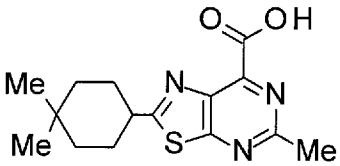
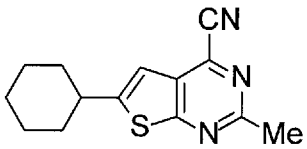
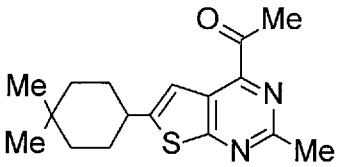
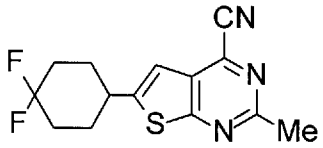
[0181]

[Table 12]

No. /Inf	Str	No	Str
Pr13		Pr15-2	
Pr14		Pr16	
Pr14-1		Pr16-1	
Pr15		Pr17	
Pr15-1 Chiral		Pr17-1	

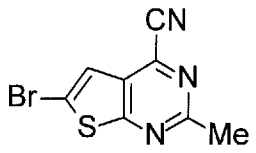
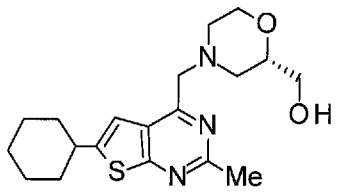
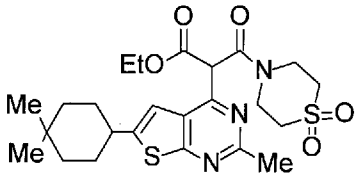
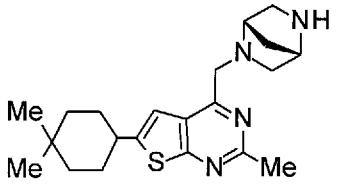
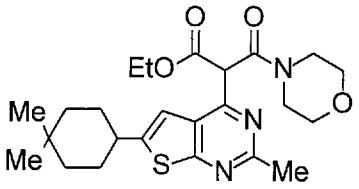
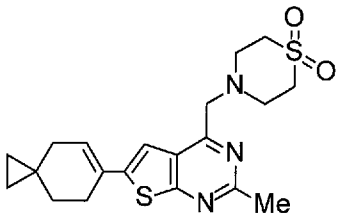
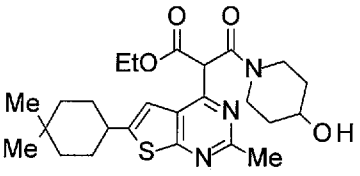
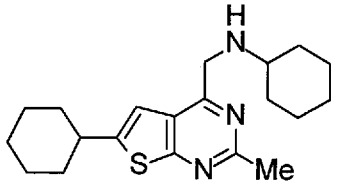
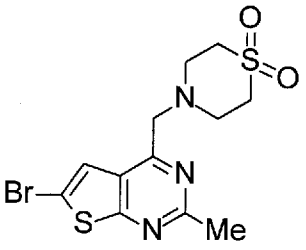
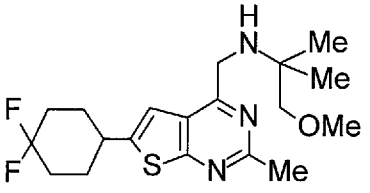
[0182]

[Table 13]

No. /Inf	Str	No. /Inf	Str
Pr17-2		Pr21	
Pr18		Pr22	
Pr18-1		Pr23	
Pr19		Pr24	
Pr20		Pr24-1	

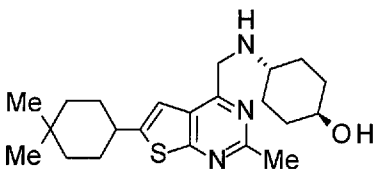
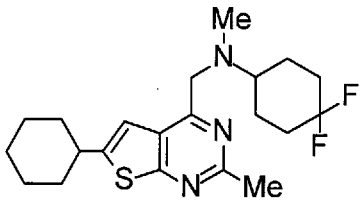
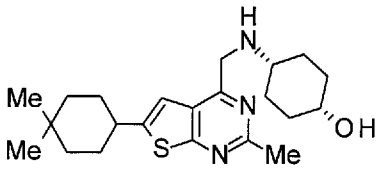
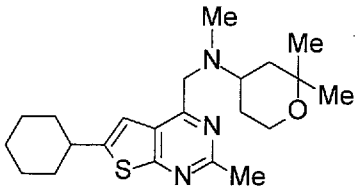
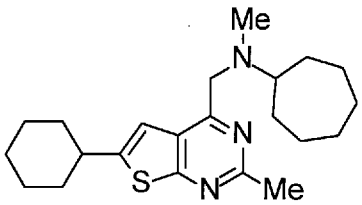
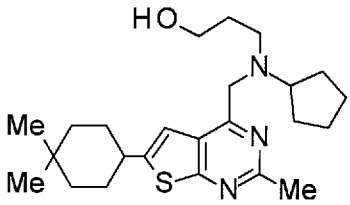
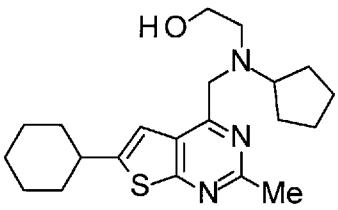
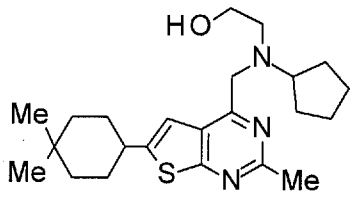
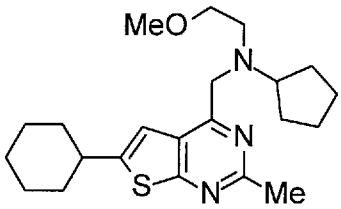
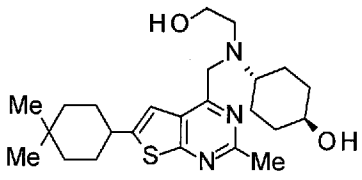
[0183]

[Table 14]

No. /Inf	Str	No. /Inf	Str
Pr24-2		Pr26-1 Chiral	
Pr25		Pr27 /2HCl	
Pr25-1		Pr28	
Pr25-2		Pr29	
Pr26		Pr30	

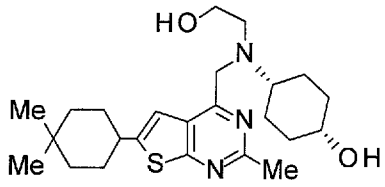
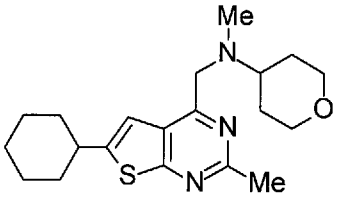
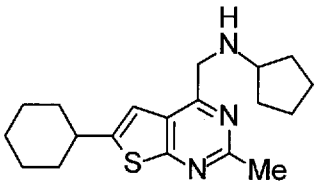
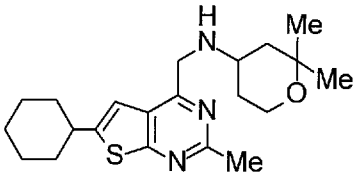
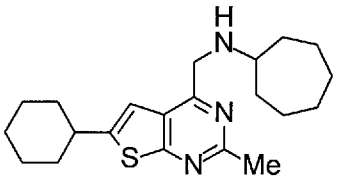
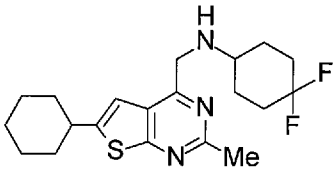
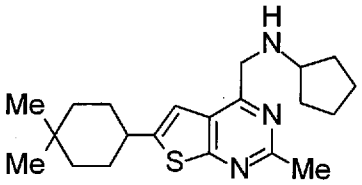
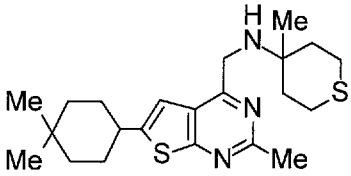
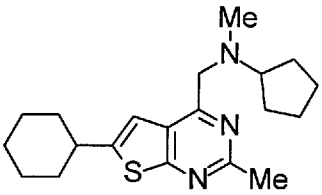
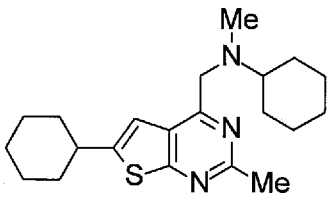
[0184]

[Table 15]

No. /Inf	Str	No. /Inf	Str
Pr30-1		Pr31-3	
Pr30-2		Pr31-4	
Pr31		Pr32	
Pr31-1		Pr32-1	
Pr31-2		Pr32-2	

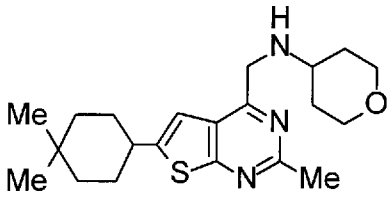
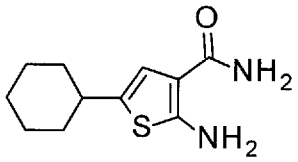
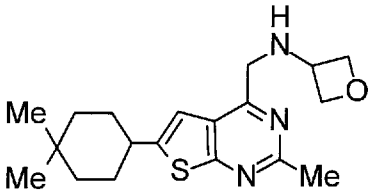
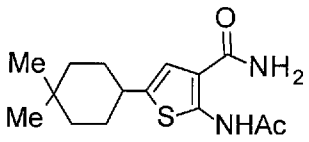
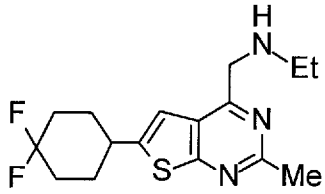
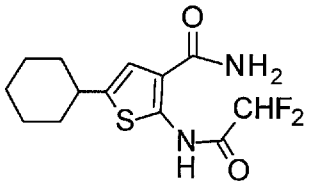
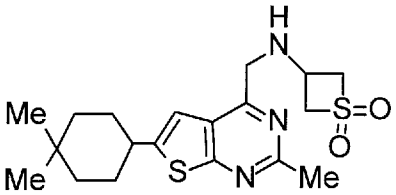
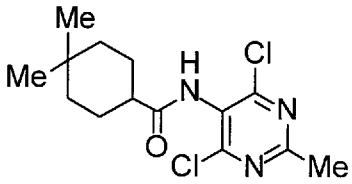
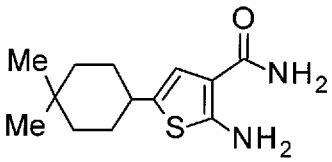
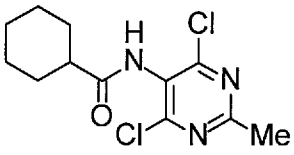
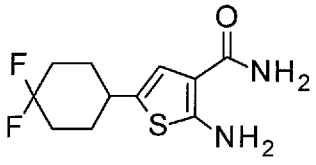
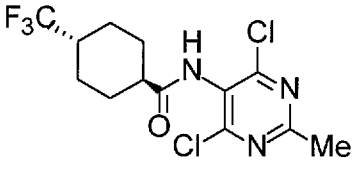
[0185]

[Table 16]

No. /Inf	Str	No. /Inf	Str
Pr32-3		Pr34-1	
Pr33		Pr34-2	
Pr33-1		Pr34-3	
Pr33-2		Pr34-4	
Pr34		Pr34-5	

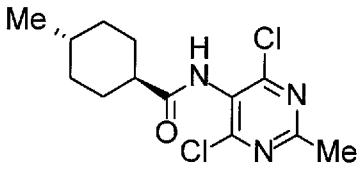
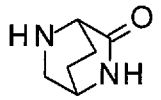
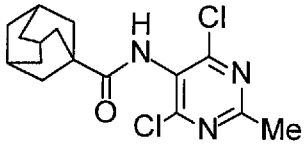
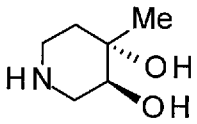
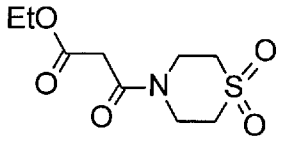
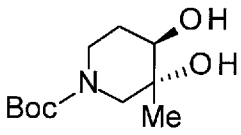
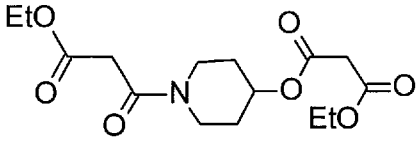
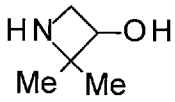
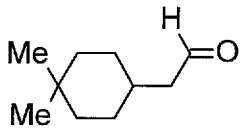
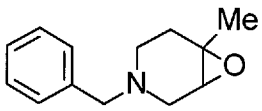
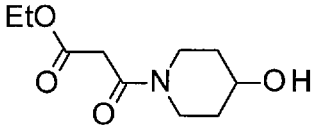
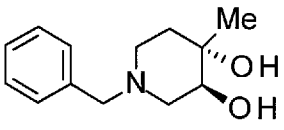
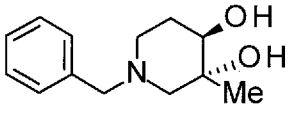
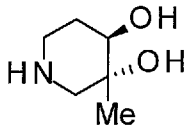
[0186]

[Table 17]

No. /Inf	Str	No. /Inf	Str
Pr34-6		Pr37-2	
Pr34-7		Pr38	
Pr35 /HCl		Pr39	
Pr36 /HCl		Pr40	
Pr37		Pr40-1	
Pr37-1		Pr40-2	

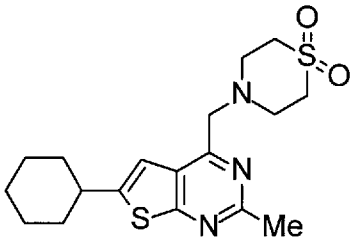
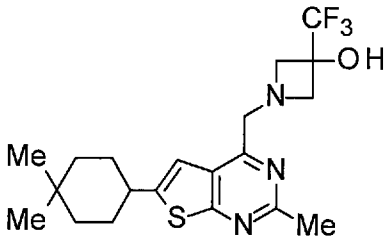
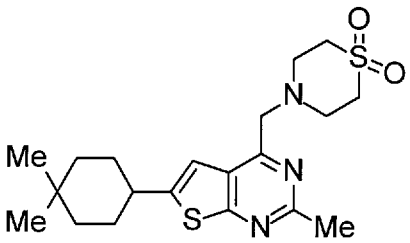
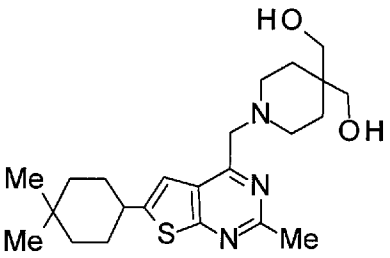
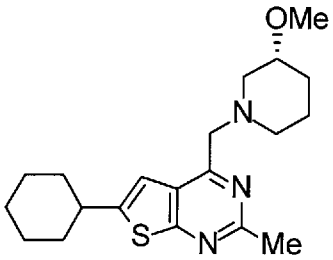
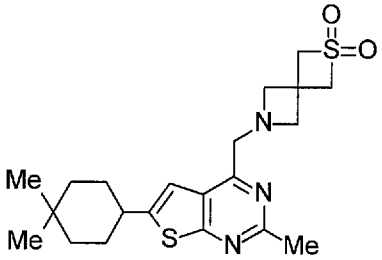
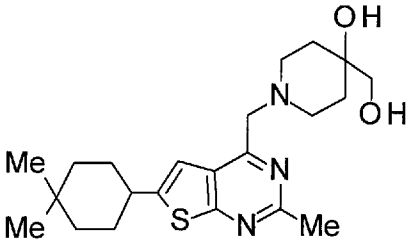
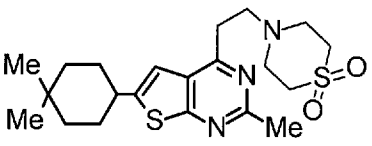
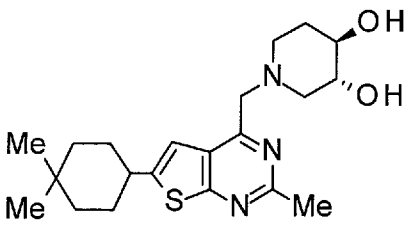
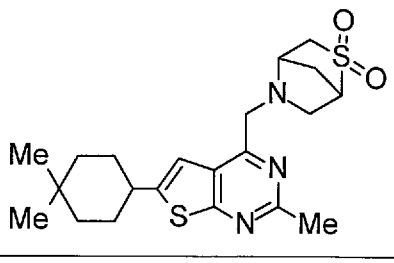
[0187]

[Table 18]

No. /Inf	Str	No. /Inf	Str
Pr40-3		Pr46	
Pr41		Pr47 /AcOH	
Pr42		Pr48	
Pr42-1		Pr49	
Pr43		Pr50	
Pr44		Pr51 /AcOH	
Pr45		Pr52 /HCl	

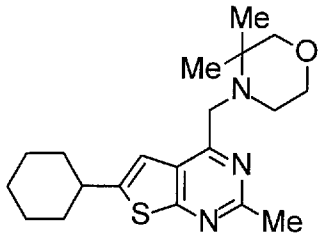
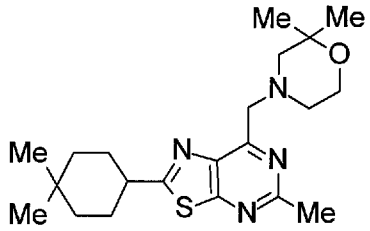
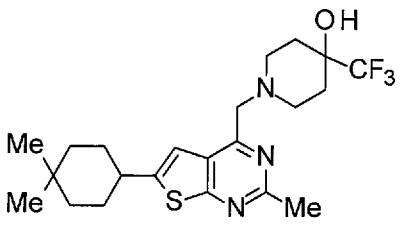
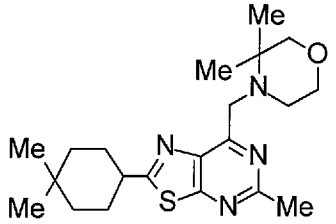
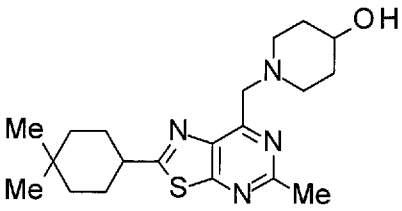
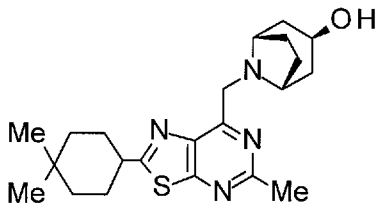
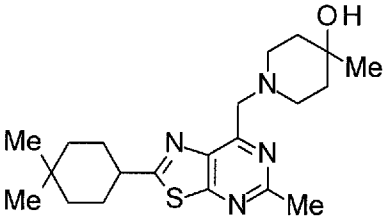
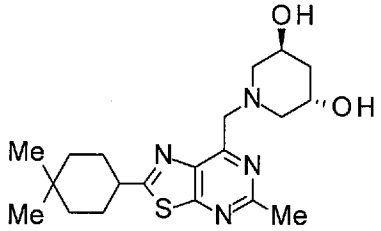
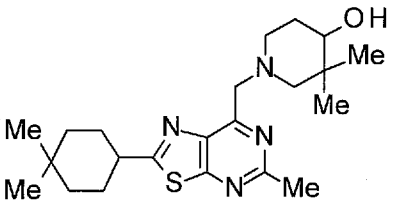
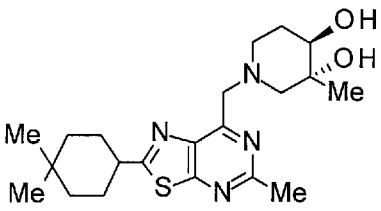
[0188]

[Table 19]

No. /Inf	Str	No. /Inf	Str
Ex1		Ex6	
Ex2		Ex7	
Ex3 Chiral		Ex8	
Ex4		Ex9	
Ex5		Ex10	

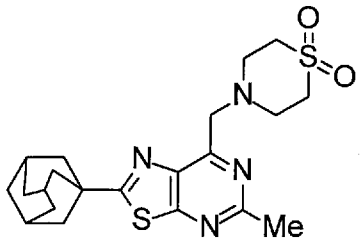
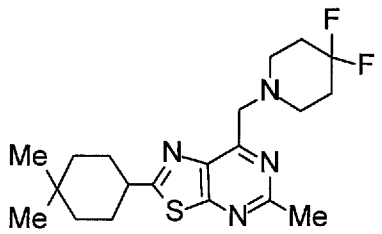
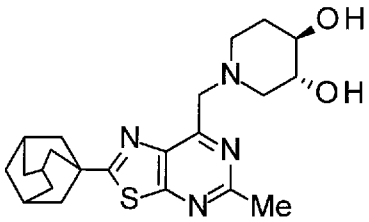
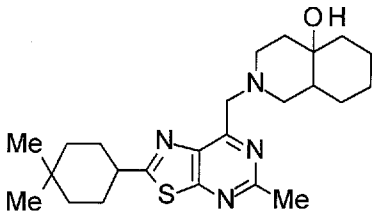
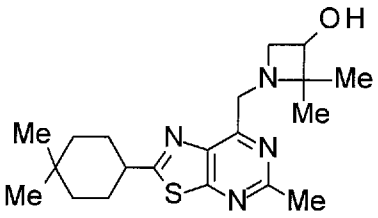
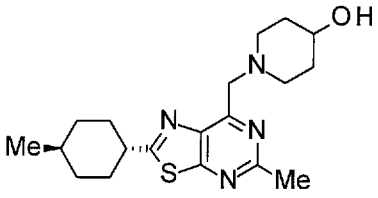
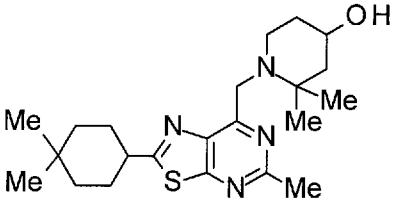
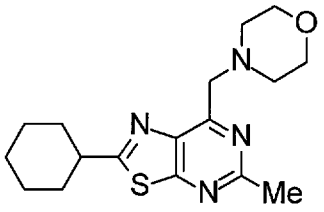
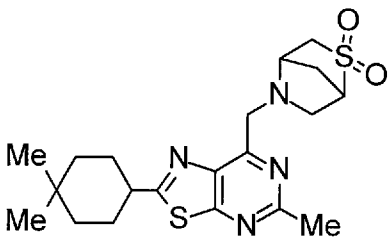
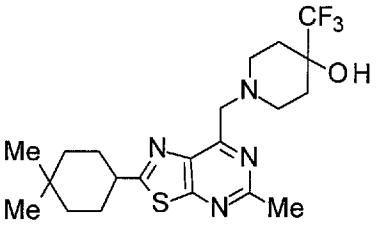
[0189]

[Table 20]

No. /Inf	Str	No. /Inf	Str
Ex11		Ex16	
Ex12		Ex17	
Ex13		Ex18	
Ex14		Ex19 Chiral	
Ex15		Ex20	

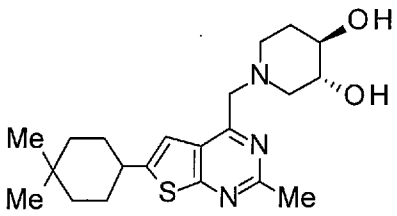
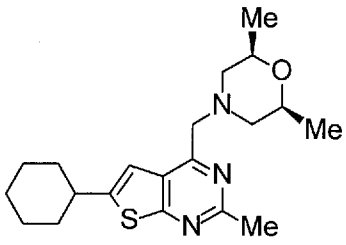
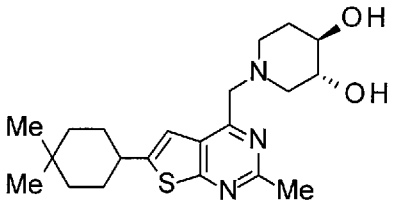
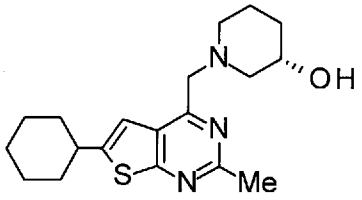
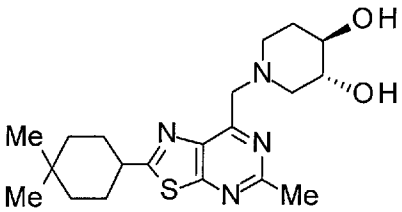
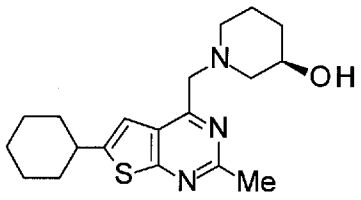
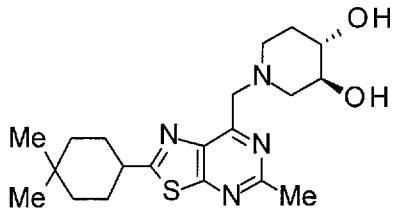
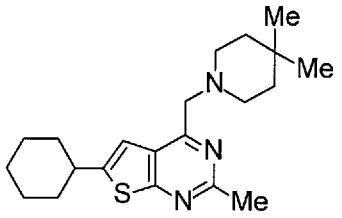
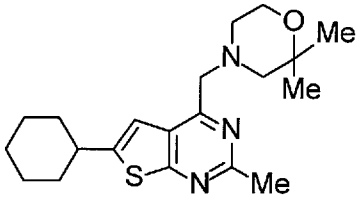
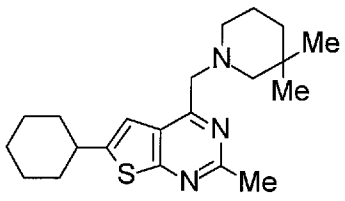
[0190]

[Table 21]

No. /Inf	Str	No. /Inf	Str
Ex21		Ex26	
Ex22		Ex27	
Ex23		Ex28	
Ex24		Ex29	
Ex25		Ex30	

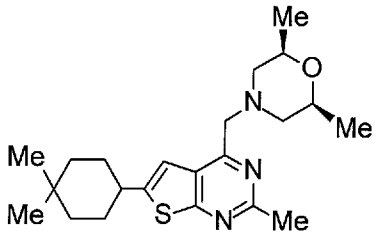
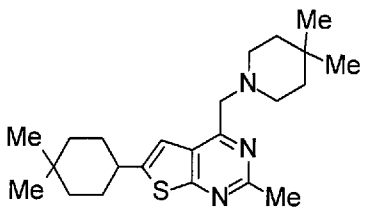
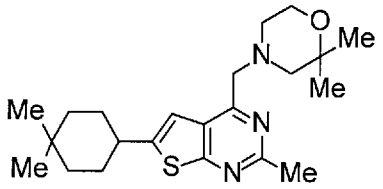
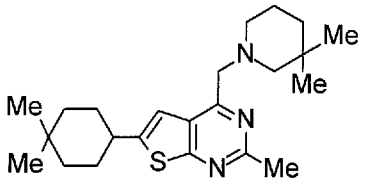
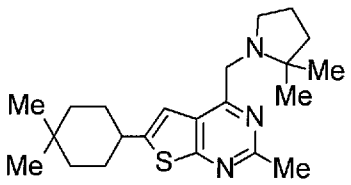
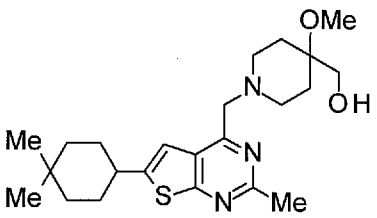
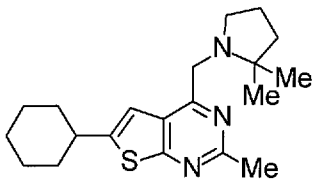
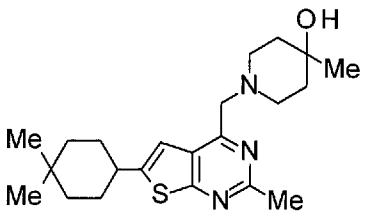
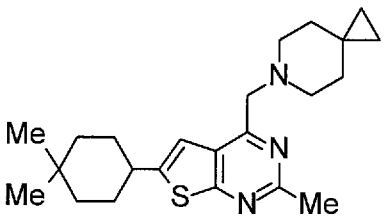
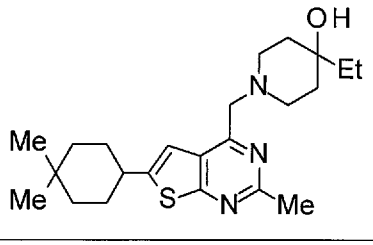
[0191]

[Table 22]

No. /Inf	Str	No. /Inf	Str
Ex31 Chiral		Ex34 /HCl	
Ex31-1 Chiral		Ex35 /HCl Chiral	
Ex32 Chiral		Ex36 /HCl Chiral	
Ex32-1 Chiral		Ex37 /HCl	
Ex33 /HCl		Ex38 /HCl	

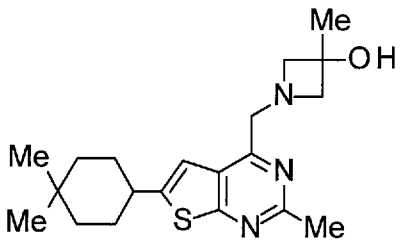
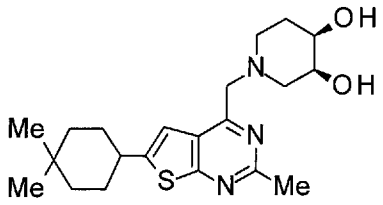
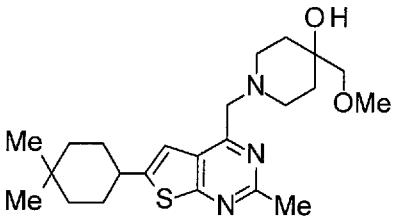
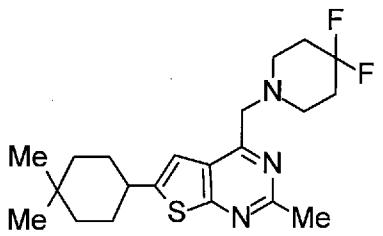
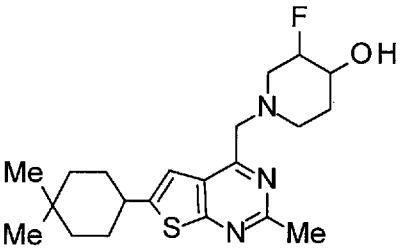
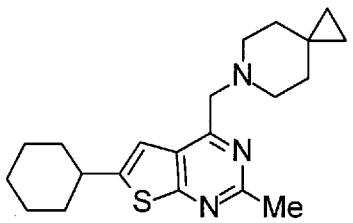
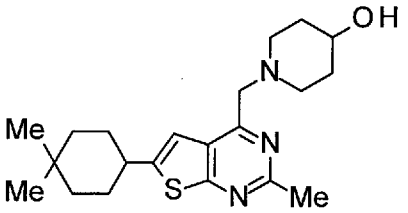
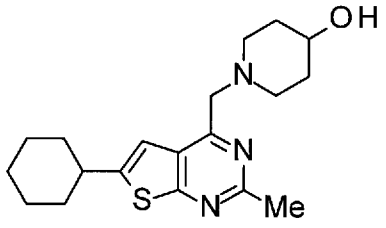
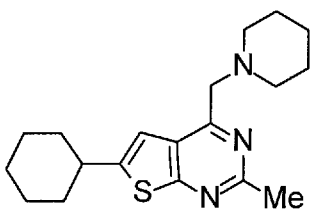
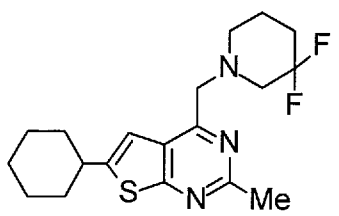
[0192]

[Table 23]

No. /Inf	Str	No. /Inf	Str
Ex39 /HCl		Ex44 /HCl	
Ex40 /HCl		Ex45 /HCl	
Ex41 /HCl		Ex46 /HCl	
Ex42 /HCl		Ex47 /HCl	
Ex43 /HCl		Ex48 /HCl	

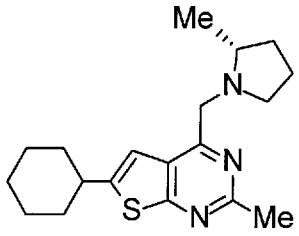
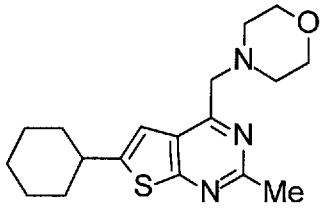
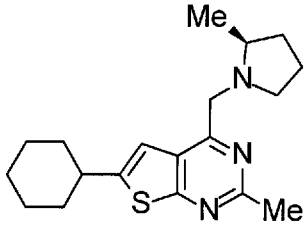
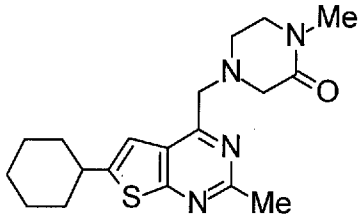
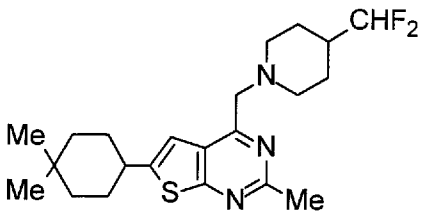
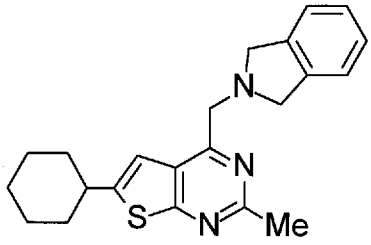
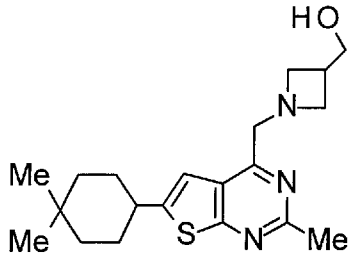
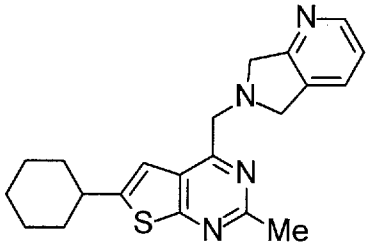
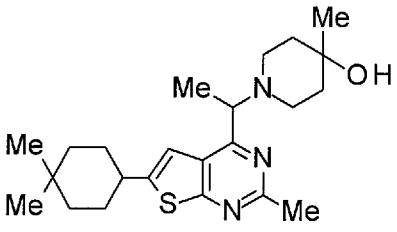
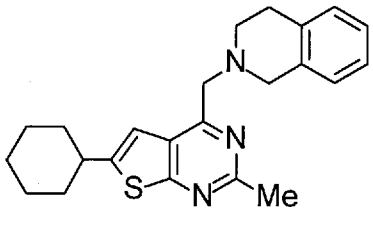
[0193]

[Table 24]

No. /Inf	Str	No. /Inf	Str
Ex49 /HCl		Ex54 /HCl	
Ex50 /HCl		Ex55 /HCl	
Ex51 /HCl		Ex56 /HCl	
Ex52 /HCl		Ex57 /HCl	
Ex53 /HCl		Ex58 /HCl	

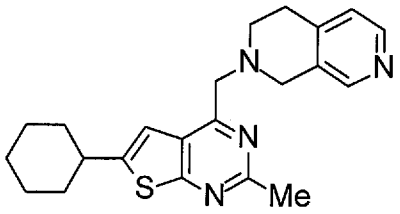
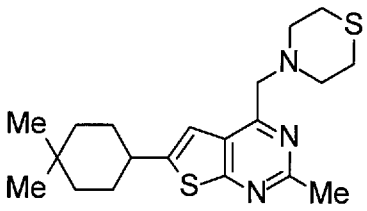
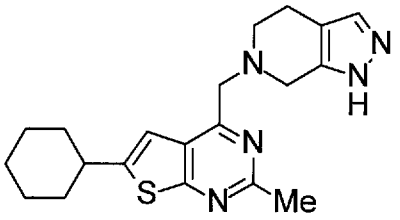
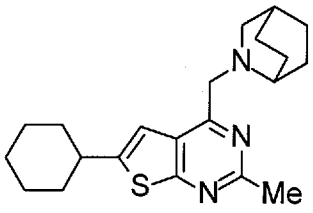
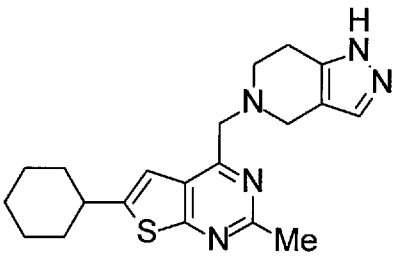
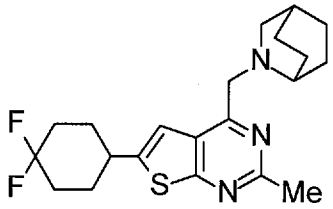
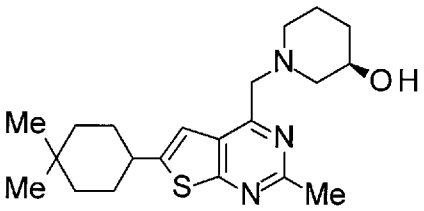
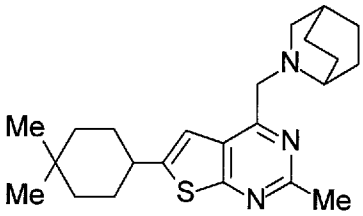
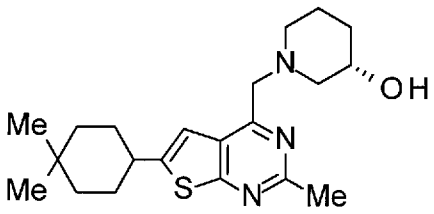
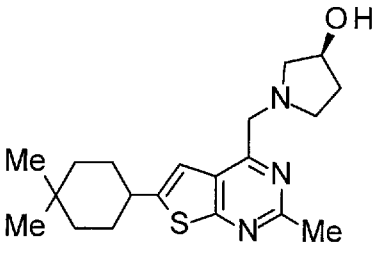
[0194]

[Table 25]

No. /Inf	Str	No. /Inf	Str
Ex59 /HCl Chiral		Ex64 /HCl	
Ex60 /HCl Chiral		Ex65 /HCl	
Ex61 /HCl		Ex66 /HCl	
Ex62 /HCl		Ex67 /2HCl	
Ex63 /HCl		Ex68 /HCl	

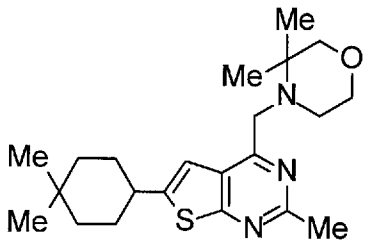
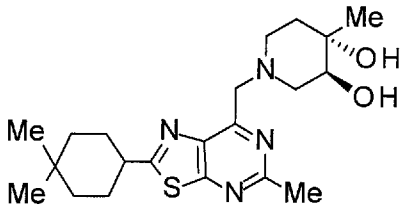
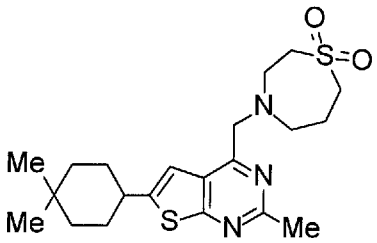
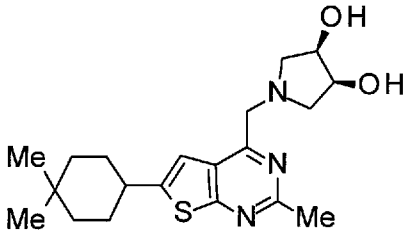
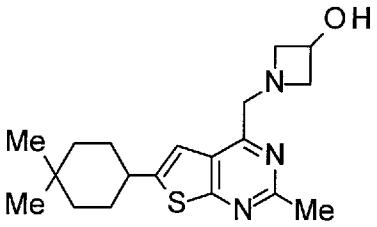
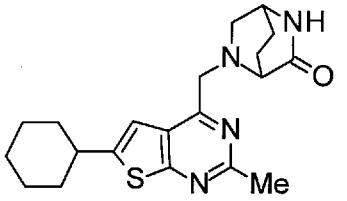
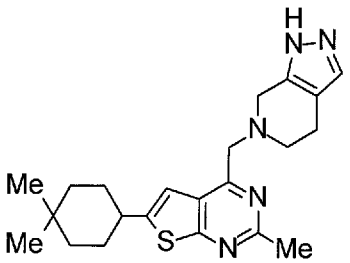
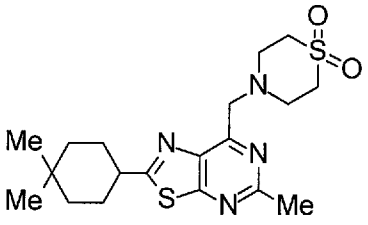
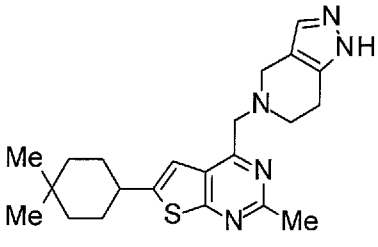
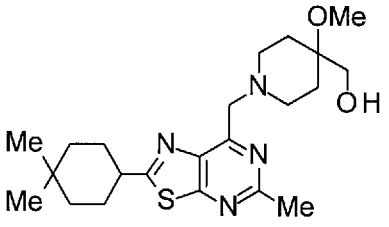
[0195]

[Table 26]

No. /Inf	Str	No. /Inf	Str
Ex69 /2HCl		Ex74 /HCl	
Ex70 /2HCl		Ex75 /HCl	
Ex71 /2HCl		Ex76 /HCl	
Ex72 /HCl Chiral		Ex77 /HCl	
Ex73 /HCl Chiral		Ex78 /HCl Chiral	

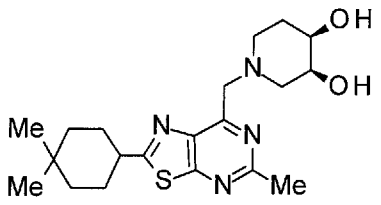
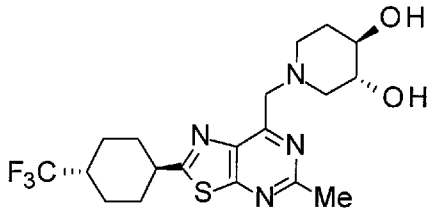
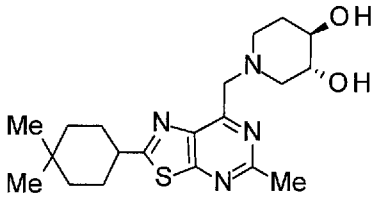
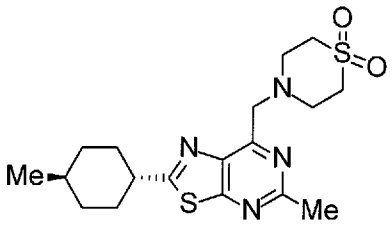
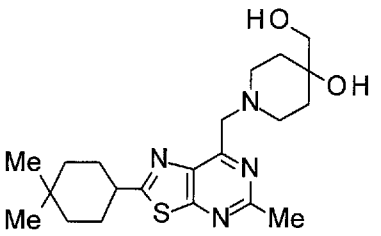
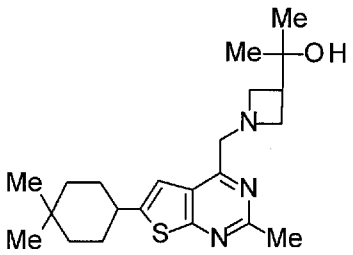
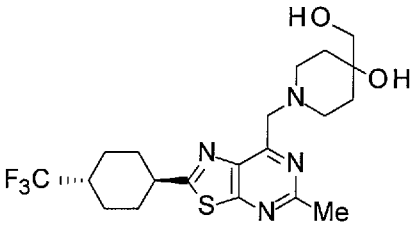
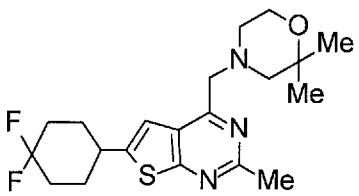
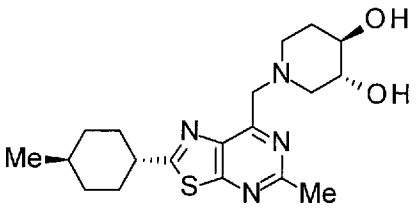
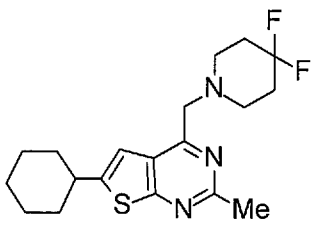
[0196]

[Table 27]

No./Inf	Str	No./Inf	Str
Ex79/HCl		Ex84/HCl	
Ex80/HCl		Ex85	
Ex81/HCl		Ex86	
Ex82/2HCl		Ex87	
Ex83/2HCl		Ex88	

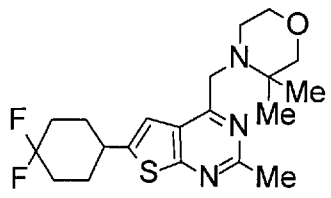
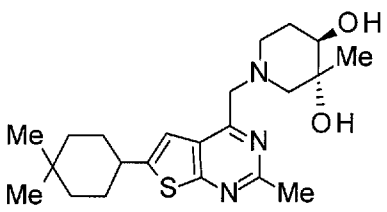
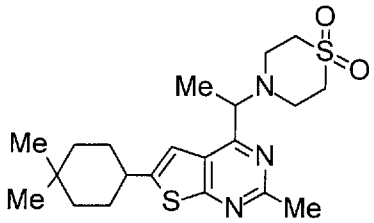
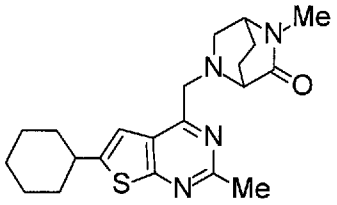
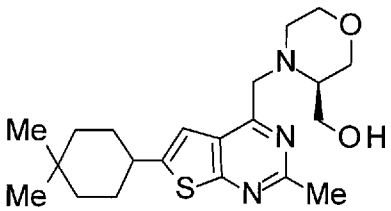
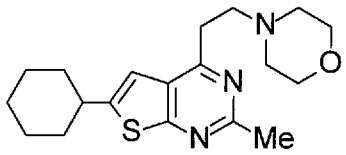
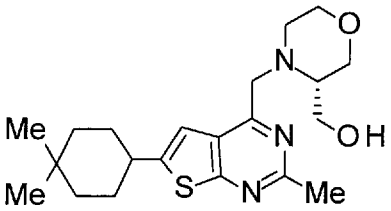
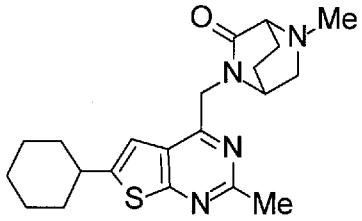
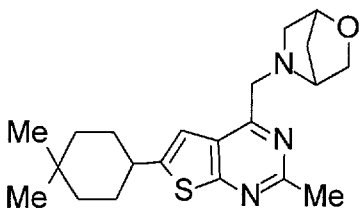
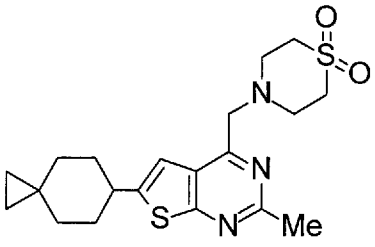
[0197]

[Table 28]

No. /Inf	Str	No. /Inf	Str
Ex89		Ex94	
Ex90		Ex95	
Ex91		Ex96 /HCl	
Ex92		Ex97 /HCl	
Ex93		Ex98 /HCl	

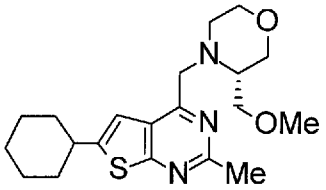
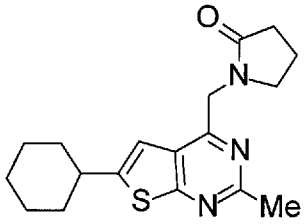
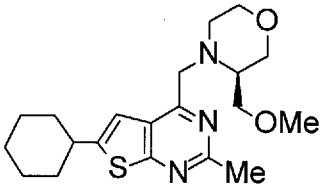
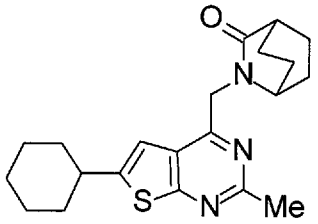
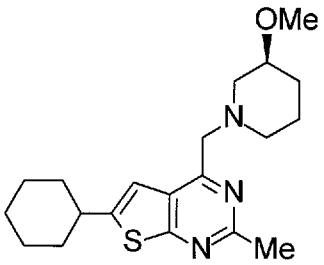
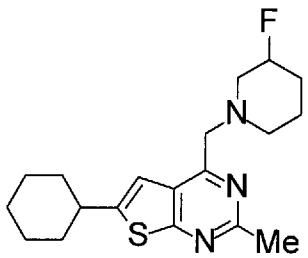
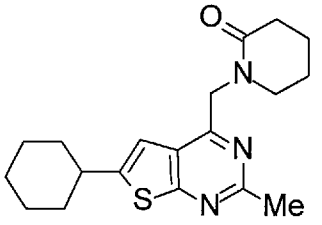
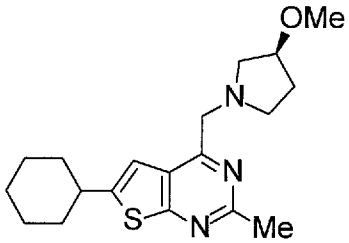
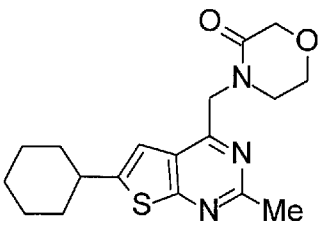
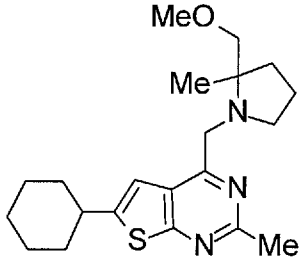
[0198]

[Table 29]

No. /Inf	Str	No. /Inf	Str
Ex99 /HCl		Ex104 /HCl	
Ex100 /HCl		Ex105 /HCl	
Ex101 /HCl Chiral		Ex106	
Ex102 /HCl Chiral		Ex107 /HCl	
Ex103 /HCl		Ex108	

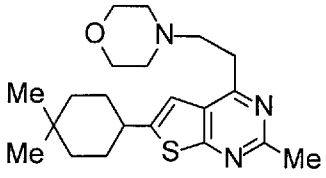
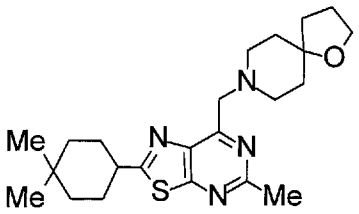
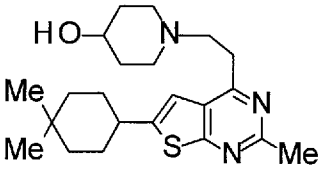
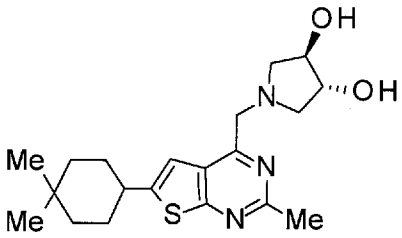
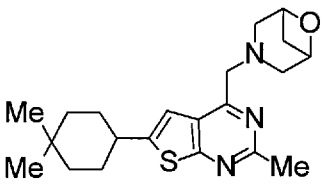
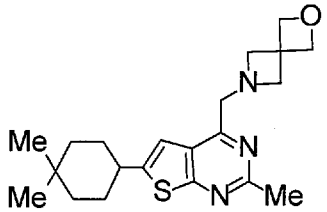
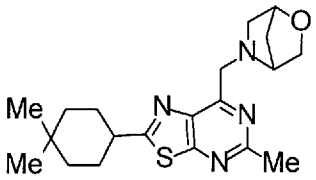
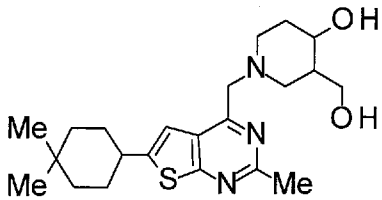
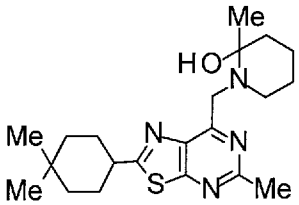
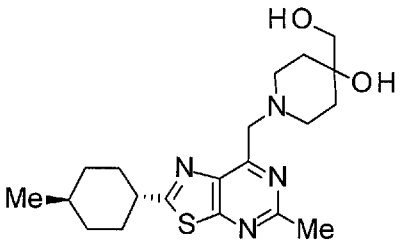
[0199]

[Table 30]

No. /Inf	Str	No. /Inf	Str
Ex109 Chiral		Ex114	
Ex110 Chiral		Ex115	
Ex111 /HCl Chiral		Ex116 /FUM	
Ex112		Ex117 /FUM Chiral	
Ex113		Ex118 /FUM	

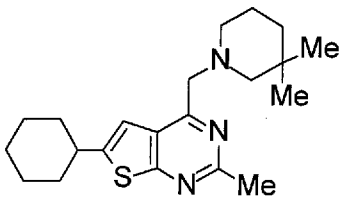
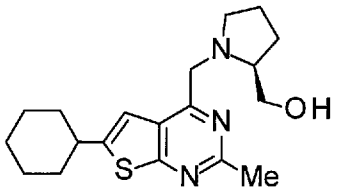
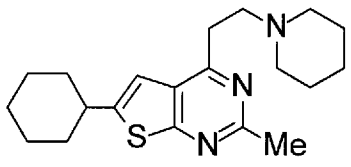
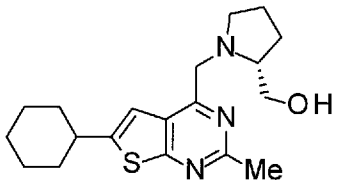
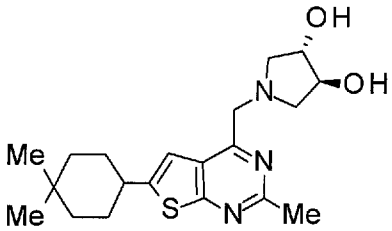
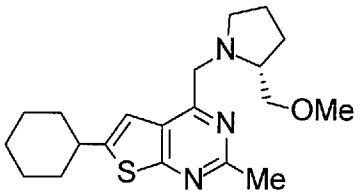
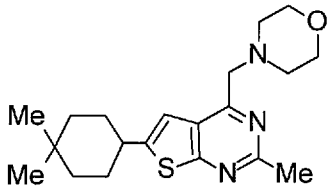
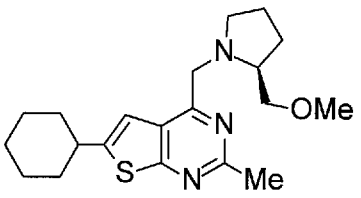
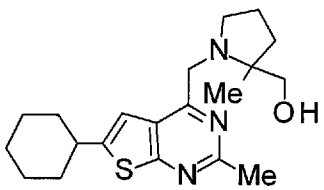
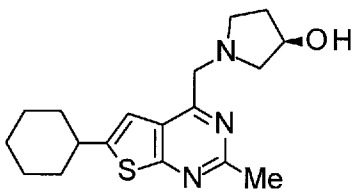
[0200]

[Table 31]

No. /Inf	Str	No. /Inf	Str
Ex119 /FUM		Ex124 /FUM	
Ex120 /FUM		Ex125 /FUM Chiral	
Ex121 /FUM		Ex126 /FUM	
Ex122 /FUM		Ex127 /FUM	
Ex123 /FUM		Ex128 /FUM	

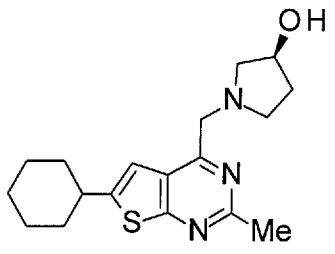
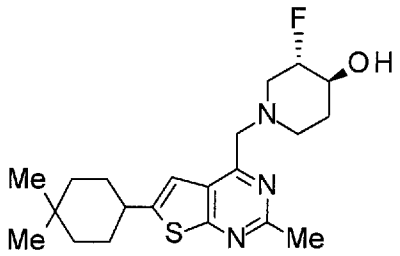
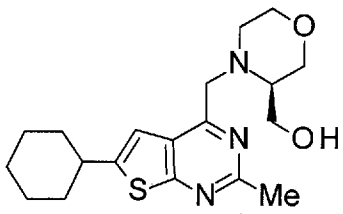
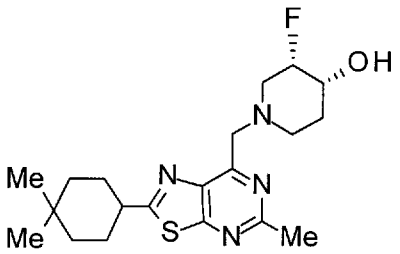
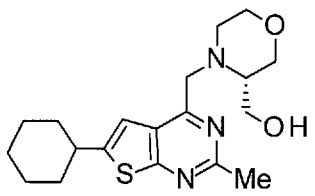
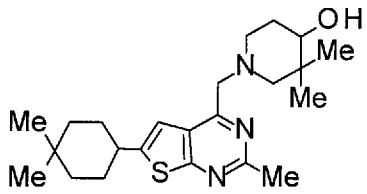
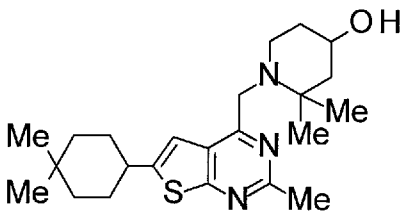
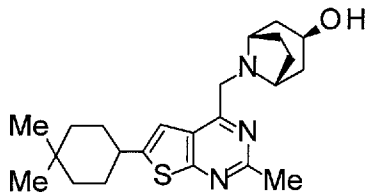
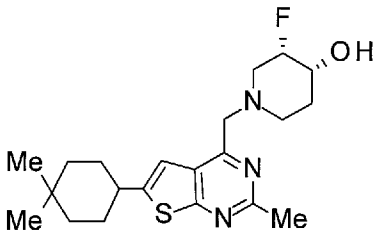
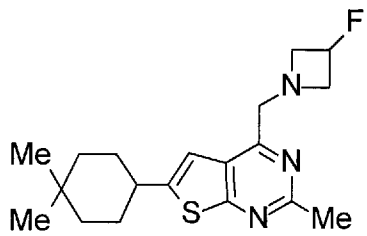
[0201]

[Table 32]

No. /Inf	Str	No. /Inf	Str
Ex129		Ex134 /FUM Chiral	
Ex130 /2HCl		Ex135 /FUM Chiral	
Ex131 /HCl Chiral		Ex136 /FUM Chiral	
Ex132 /HCl		Ex137 /FUM Chiral	
Ex133 /2HCl		Ex138 /FUM Chiral	

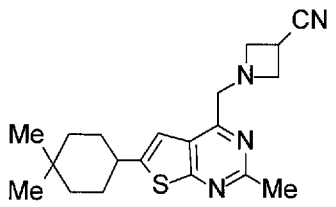
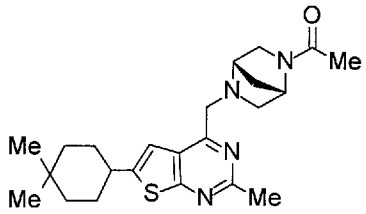
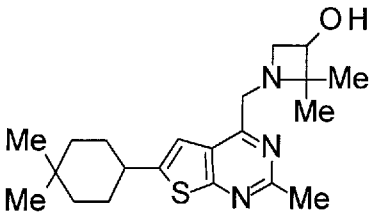
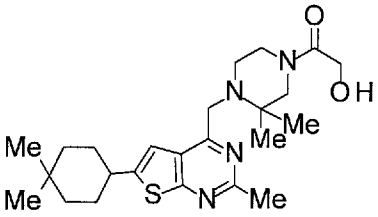
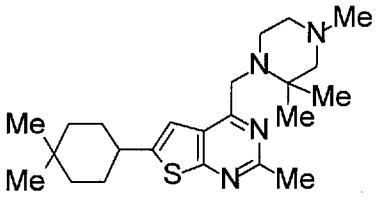
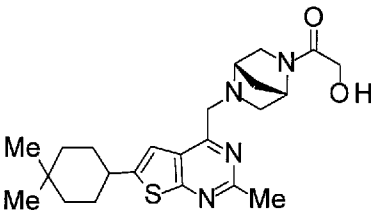
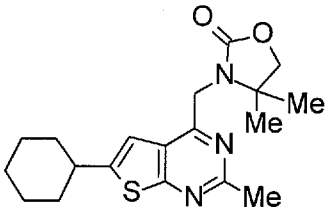
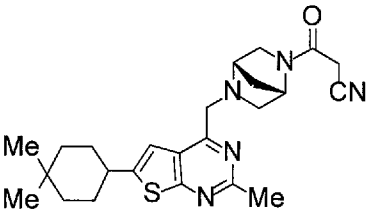
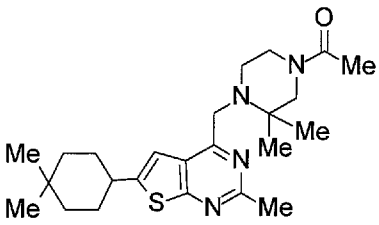
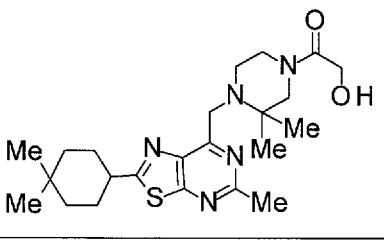
[0202]

[Table 33]

No. /Inf	Str	No. /Inf	Str
Ex139 /FUM Chiral		Ex144	
Ex140 Chiral		Ex145 Chiral	
Ex141 Chiral		Ex146 /HCl	
Ex142		Ex147 /HCl	
Ex143 Chiral		Ex148 /HCl	

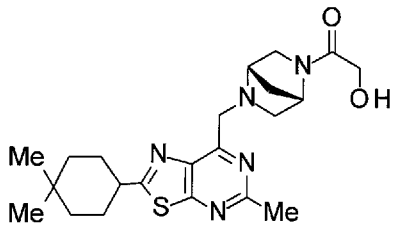
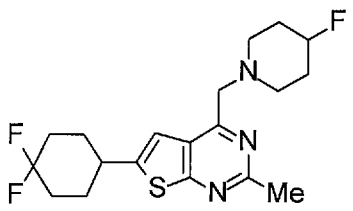
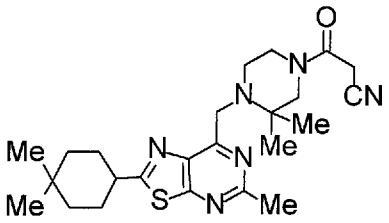
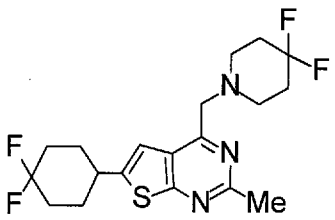
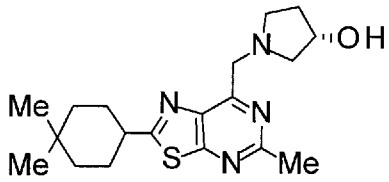
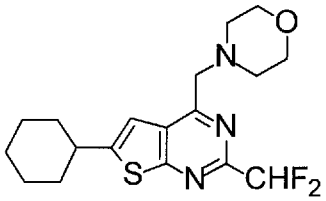
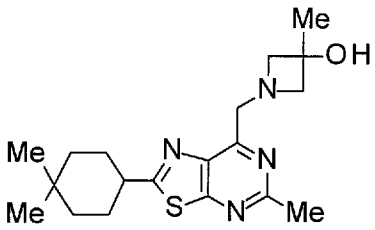
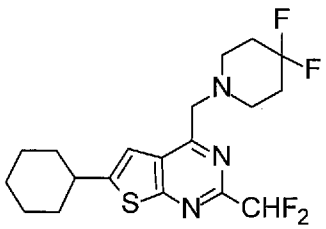
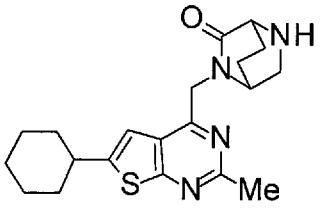
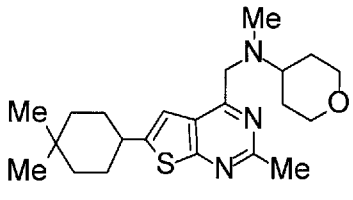
[0203]

[Table 34]

No. /Inf	Str	No. /Inf	Str
Ex149 /HCl		Ex154	
Ex150 /FUM		Ex155	
Ex151 /FUM		Ex156	
Ex152		Ex157	
Ex153 /HCl		Ex158	

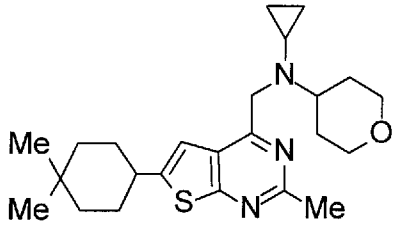
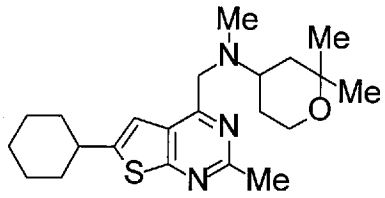
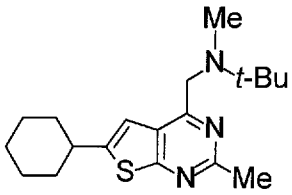
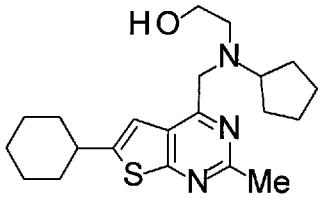
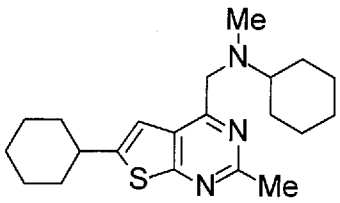
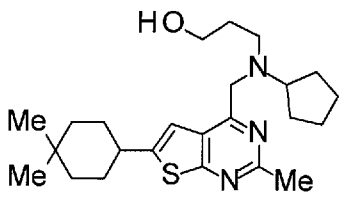
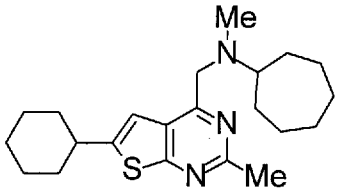
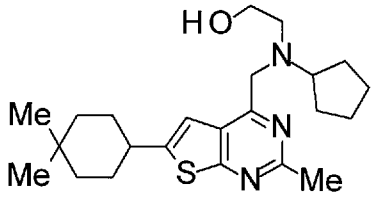
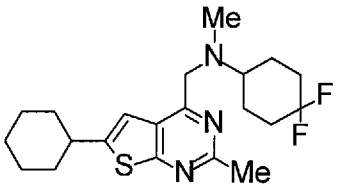
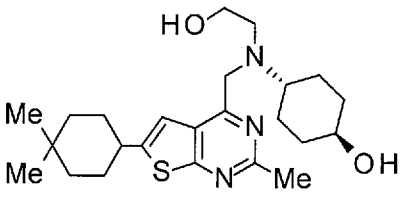
[0204]

[Table 35]

No. /Inf	Str	No. /Inf	Str
Ex159 Chiral		Ex164 /HCl	
Ex160		Ex165 /HCl	
Ex161 /FUM Chiral		Ex166 /HCl	
Ex162 /FUM		Ex167 /HCl	
Ex163		Ex168	

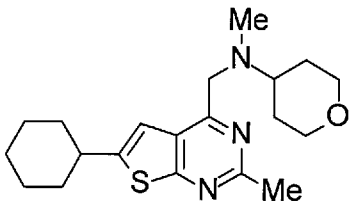
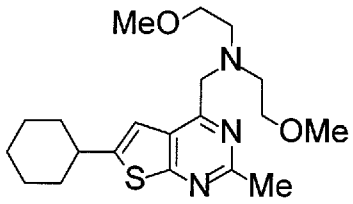
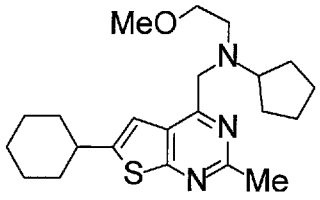
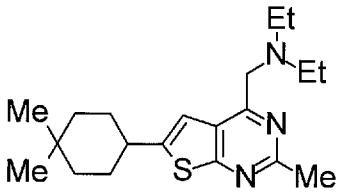
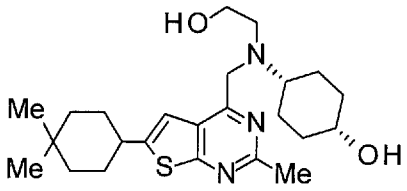
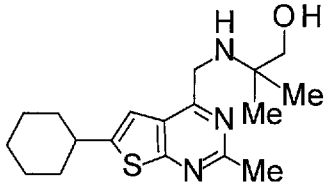
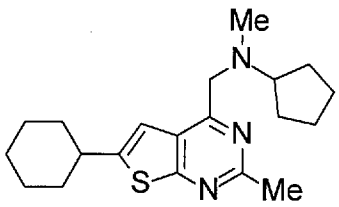
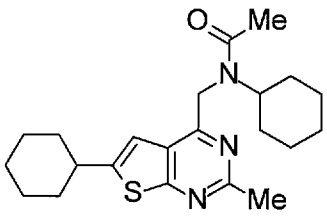
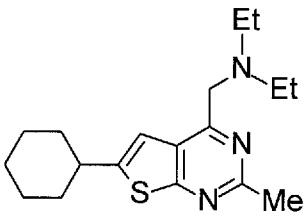
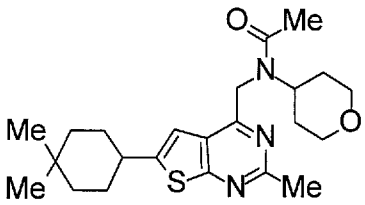
[0205]

[Table 36]

No. /Inf	Str	No. /Inf	Str
Ex169		Ex174 /HCl	
Ex170		Ex175 /HCl	
Ex171 /HCl		Ex176 /HCl	
Ex172 /HCl		Ex177 /HCl	
Ex173 /HCl		Ex178 /HCl	

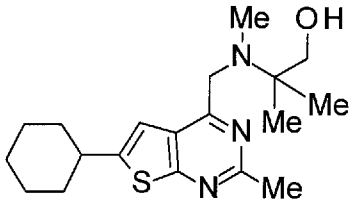
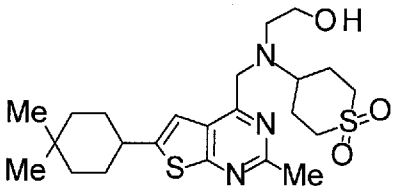
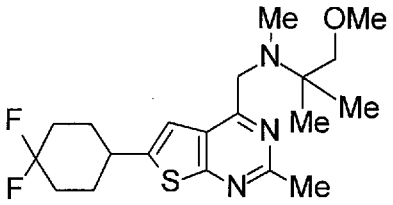
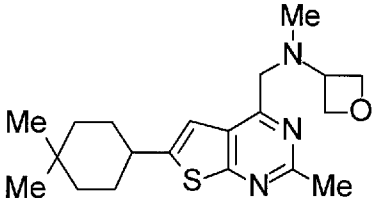
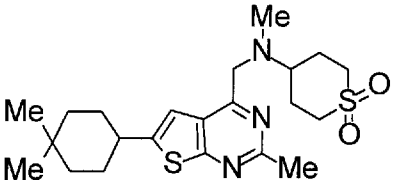
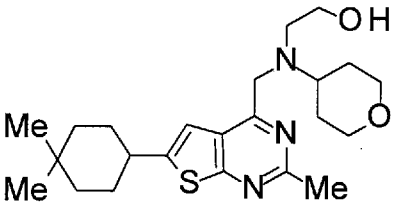
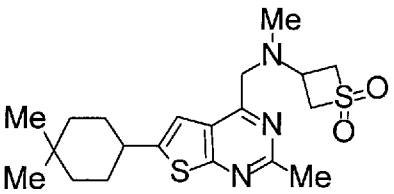
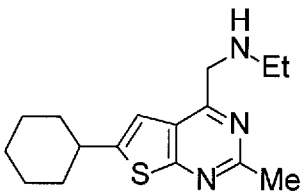
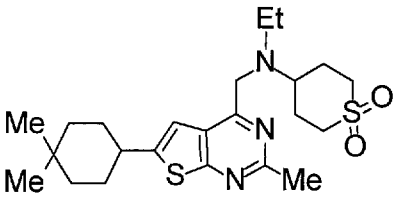
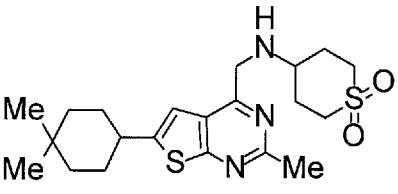
[0206]

[Table 37]

No. /Inf	Str	No. /Inf	Str
Ex179 /HCl		Ex184 /HCl	
Ex180 /HCl		Ex185 /HCl	
Ex181 /HCl		Ex186	
Ex182 /HCl		Ex187	
Ex183 /HCl		Ex188	

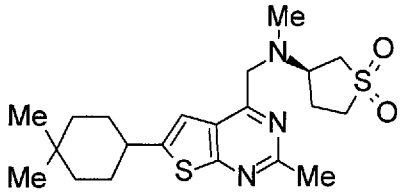
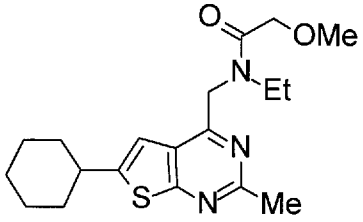
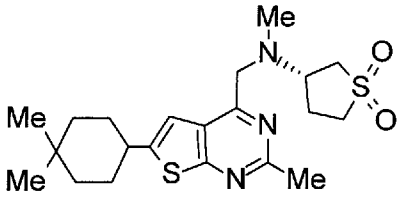
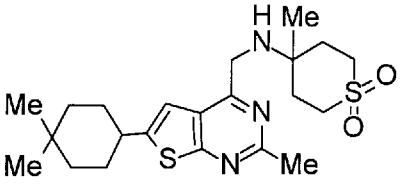
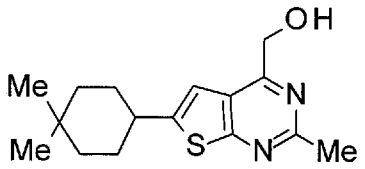
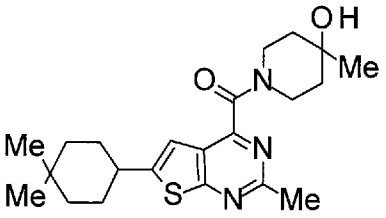
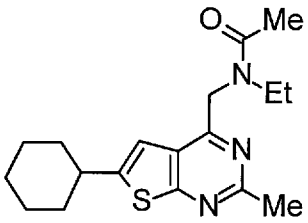
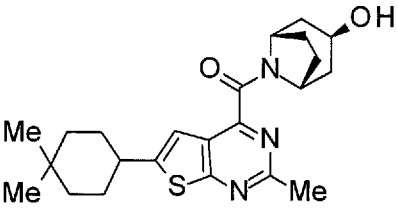
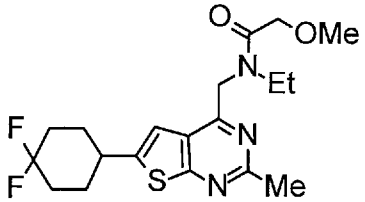
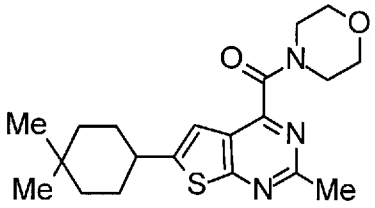
[0207]

[Table 38]

No. /Inf	Str	No. /Inf	Str
Ex189		Ex194	
Ex190 /FUM		Ex195	
Ex191 /HCl		Ex196	
Ex192 /HCl		Ex197 /HCl	
Ex193 /HCl		Ex198 /HCl	

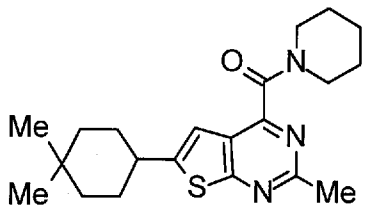
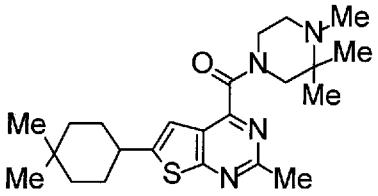
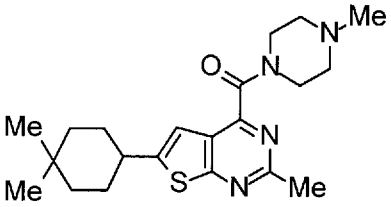
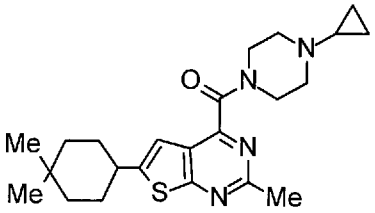
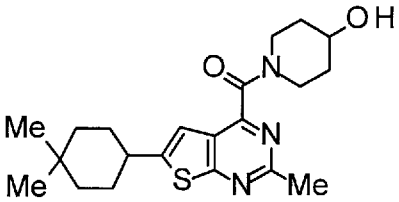
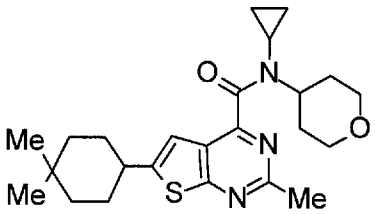
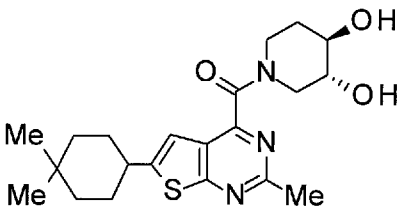
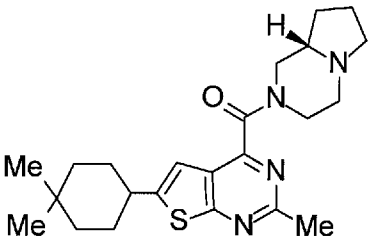
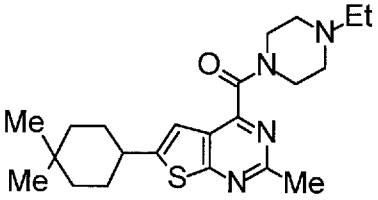
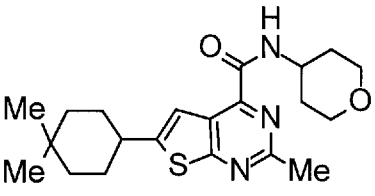
[0208]

[Table 39]

No. /Inf	Str	No. /Inf	Str
Ex199 /HCl Chiral		Ex204	
Ex200 /HCl Chiral		Ex205 /HCl	
Ex201		Ex206	
Ex202		Ex207	
Ex203		Ex208	

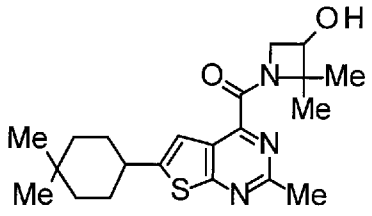
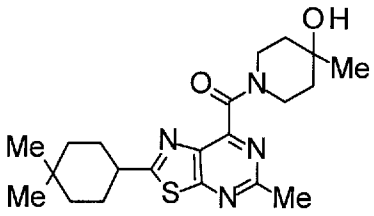
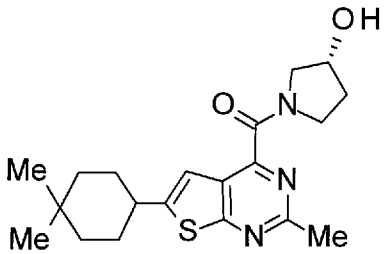
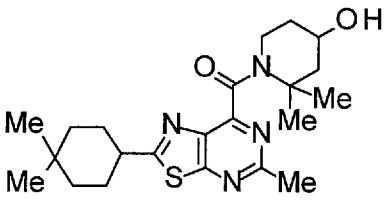
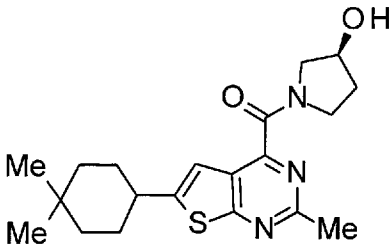
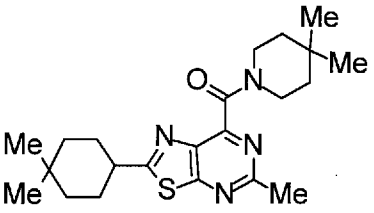
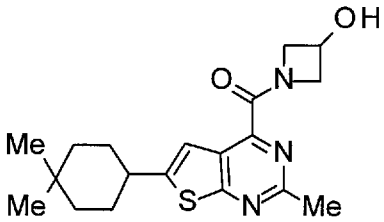
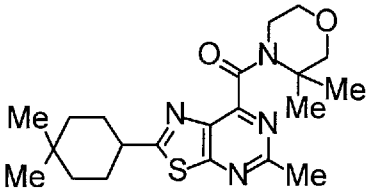
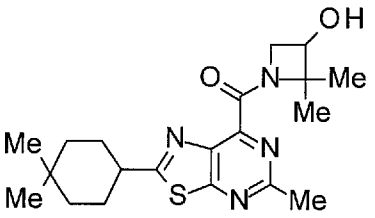
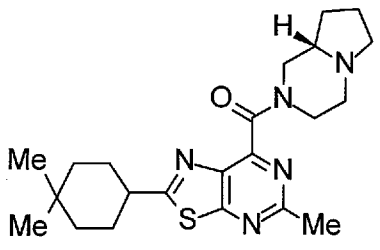
[0209]

[Table 40]

No./Inf	Str	No./Inf	Str
Ex209		Ex214	
Ex210		Ex215	
Ex211		Ex216	
Ex212		Ex217 Chiral	
Ex213		Ex218	

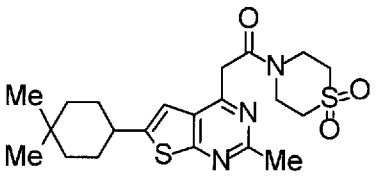
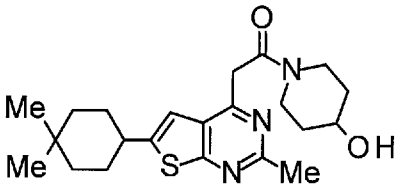
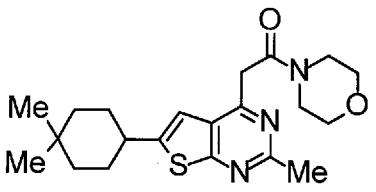
[0210]

[Table 41]

No. /Inf	Str	No. /Inf	Str
Ex219		Ex224	
Ex220 Chiral		Ex225	
Ex221 Chiral		Ex226	
Ex222		Ex227	
Ex223		Ex228 Chiral	

[0211]

[Table 42]

No. /Inf	Str	No. /Inf	Str
Ex229		Ex231	
Ex230			

[0212]

[Table 43]

No.	Ref	Data
Pr1	Ex1	ESI+:418
Pr1-1	Ex1	ESI+:360
Pr1-2	Ex1	ESI+:360
Pr1-3	Ex1	
Pr1-4	Ex1	ESI+:358
Pr1-5	Ex1	ESI+:388
Pr1-6	Ex1	ESI+:388
Pr1-7	Ex1	ESI+:372
Pr1-8	Ex1	ESI+:344
Pr1-9	Ex1	ESI+:384
Pr1-10	Ex1	ESI+:386
Pr1-11	Ex1	ESI+:386
Pr1-12	Ex1	ESI+:418
Pr1-13	Ex1	ESI+:388
Pr1-14	Ex1	ESI+:402
Pr1-15	Ex1	ESI+:360
Pr1-16	Ex1	ESI+:361

[0213]

[Table 44]

No.	Ref	Data
Pr1-17	Ex1	ESI+:361
Pr1-18	Ex1	ESI+:346
Pr2	Pr34	
Pr2-1	Pr34	ESI+:487
Pr2-2	Pr34	ESI+:392
Pr2-3	Pr34	ESI+:488
Pr2-4	Pr34	ESI+:472
Pr3	Pr3	ESI+:277
Pr3-1	Pr3	ESI+:285
Pr4	Pr4	ESI+:267
Pr4-1	Pr4-1	ESI+:295
Pr4-2	Pr4	ESI+:263,265
Pr4-3	Pr4	EI:218,220
Pr4-4	Pr4	ESI+:303,305
Pr4-5	Pr4	ESI+:303
Pr4-6	Pr4-6	ESI+:296,298
Pr4-7	Pr4	ESI+:268,270
Pr4-8	Pr4	ESI+:320
Pr4-9	Pr4-6	ESI+:336,338
Pr4-10	Pr4-6	ESI+:282,284
Pr5	Pr5	ESI+:286
Pr5-1	Pr5	ESI+:294
Pr6	Pr6	ESI+:305
Pr6-1	Pr6-1	ESI+:333
Pr6-2	Pr6	ESI+:301,303
Pr6-3	Pr6	ESI+:341
Pr6-4	Pr6	ESI+:341
Pr7	Pr7	ESI+:263
Pr7-1	Pr7-1	ESI+:291
Pr7-2	Pr7	ESI+:259,261
Pr7-3	Pr7	ESI+:299
Pr7-4	Pr7	APCI/ESI+:299
Pr8	Pr8	ESI+:369

[0214]

[Table 45]

No.	Ref	Data
Pr8-1	Pr8	ESI+:341
Pr8-2	Pr8	
Pr8-3	Pr8	
Pr8-4	Pr8	
Pr8-5	Pr8	ESI+:377
Pr8-6	Pr8-7	ESI+:356
Pr8-7	Pr8-7	ESI+:370
Pr8-8	Pr8	
Pr8-9	Pr8-7	ESI+:342
Pr8-10	Pr8-7	ESI+:410
Pr9	Pr9	ESI+:278
Pr9-1	Pr9	ESI+:250
Pr9-2	Pr9	ESI+:302
Pr9-3	Pr9	ESI+:318
Pr9-4	Pr9	ESI+:264
Pr10	Pr10	ESI+:396
Pr10-1	Pr10	ESI+:368
Pr10-2	Pr10	ESI+:420
Pr10-3	Pr10	ESI+:436
Pr10-4	Pr10	ESI+:382
Pr11	Pr11	ESI+:292
Pr11-1	Pr11	ESI+:264
Pr11-2	Pr11	ESI+:278
Pr11-3	Pr11	ESI+:332
Pr12	Pr12	ESI+:249
Pr12-1	Pr12	ESI+:285
Pr13	Pr13	ESI+:281,283
Pr14	Pr14	ESI+:303
Pr14-1	Pr14	ESI+:331
Pr15	Pr15	ESI+:387
Pr15-1	Pr15-1	ESI+:372
Pr15-2	Pr15-1	ESI+:388
Pr16	Pr16	ESI+:275

[0215]

[Table 46]

No.	Ref	Data
Pr16-1	Pr16	ESI+:303
Pr17	Pr17	ESI+:277
Pr17-1	Pr17	ESI+:305
Pr17-2	Pr17	ESI+:305
Pr18	Pr18	ESI+:305
Pr18-1	Pr18	ESI+:316
Pr19	Pr19	ESI+:306
Pr20	Pr20	
Pr21	Ex112	ESI+:461
Pr22	Pr22	ESI+:259,261
Pr23	Pr23	ESI+:201,203
Pr24	Pr24	ESI+:258
Pr24-1	Pr24	ESI+:294
Pr24-2	Pr24	ESI+:254,256
Pr25	Pr25	ESI+:508
Pr25-1	Pr25	APCI/ESI+:460
Pr25-2	Pr25	ESI+:474
Pr26	Pr8+Ex1	ESI+:376,378
Pr26-1	Pr8+Ex1	ESI+: 362
Pr27	Pr15	ESI+:371
Pr28	Pr28	ESI+:404
Pr29	Ex1	APCI/ESI+:344
Pr30	Ex85	ESI+:384
Pr30-1	Ex85	ESI+:388
Pr30-2	Ex85	ESI+:388
Pr31	Pr31	ESI+:372
Pr31-1	Pr31	ESI+:374
Pr31-2	Pr31	ESI+:388
Pr31-3	Pr31	ESI+:394
Pr31-4	Pr31	ESI+:388
Pr32	Pr32	ESI+:416
Pr32-1	Pr32	ESI+:402
Pr32-2	Pr32	ESI+:432

[0216]

[Table 47]

No.	Ref	Data
Pr32-3	Pr32	ESI+:432
Pr33	Pr33	ESI+:330
Pr33-1	Pr33	ESI+:358
Pr33-2	Pr33	ESI+:358
Pr34	Pr34	ESI+:344
Pr34-1	Pr34	ESI+:360
Pr34-2	Pr34	ESI+:374
Pr34-3	Pr34	ESI+:380
Pr34-4	Pr34	APCI/ESI+:404
Pr34-5	Pr34	ESI+:358
Pr34-6	Pr34	ESI+:374
Pr34-7	Pr34	ESI+:346
Pr35	Ex130	ESI+:326
Pr36	Ex198	ESI+:394
Pr37	Pr37	ESI+:253
Pr37-1	Pr37	ESI+:261
Pr37-2	Pr37	ESI+:225
Pr38	Pr38	ESI+:295
Pr39	Pr39	ESI+:303
Pr40	Pr40	ESI+:316,318
Pr40-1	Pr40	ESI+:288,290
Pr40-2	Pr40	ESI+:356,358
Pr40-3	Pr40	ESI-:300,302
Pr41	Pr41	ESI+:340
Pr42	Pr42	
Pr42-1	Pr42	ESI+:330
Pr43	Pr43	CI+:155
Pr44	Pr44	ESI+:216
Pr45	Pr45	ESI+:222
Pr46	Pr46	ESI+:127
Pr47	Pr47	ESI+:132

[0217]

[Table 48]

No.	Ref	Data
Pr48	Pr48	ESI+:254
Pr49	Pr49	NMR($CDCl_3$):4.20(1H,dd,J=6.8,6.8Hz),3.64(1H,dd,J=6.8,8.9Hz),3.31(1H,dd,J=6.8,8.9Hz),1.30(3H,s),1.27(3H,s)
Pr50	Pr50	
Pr51	Pr51	ESI+:222
Pr52	Pr52	ESI+:132

[0218]

[Table 49]

No.	Ref	Data
Ex1	Ex1	ESI+:380
Ex2	Ex2	ESI+:408 NMR(DMSO-d_6):7.56(1H,d,J=1.1Hz),4.03(2H,s),3.18-3.07(4H,m),3.04-2.97(4H,m),2.93-2.85(1H,m),2.66(3H,s),1.94-1.86(2H,m),1.71-1.59(2H,m),1.53-1.44(2H,m),1.42-1.30(2H,m),0.95(6H,s)
Ex3	Ex1	ESI+:360
Ex4	Ex1	ESI+:404
Ex5	Ex1	ESI+:390
Ex6	Ex1	ESI+:414
Ex7	Ex1	ESI+:418
Ex8	Ex1	ESI+:420
Ex9	Ex1	ESI+:422
Ex10	Ex1	ESI+:420
Ex11	Ex1	ESI+:360
Ex12	Ex1	ESI+:442
Ex13	Ex1	ESI+:375
Ex14	Ex1	ESI+:389
Ex15	Ex1	ESI+:403
Ex16	Ex1	ESI+:389
Ex17	Ex1	ESI+:389
Ex18	Ex1	ESI+:401

[0219]

[Table 50]

No.	Ref	Data
Ex19	Ex1	ESI+:391
Ex20	Ex1	ESI+:405 NMR(DMSO-d6):4.45(1H,d,J=4.0Hz),4.15(1H,s),4.00(2H,s),3.21-3.15(1H,m),3.13-3.05(1H,m),2.71(3H,s),2.70-2.64(1H,m),2.55(1H,d,J=10.2Hz),2.30-2.21(1H,m),2.07(1H,d,J=10.9Hz),2.03-1.94(2H,m),1.83-1.65(3H,m),1.53-1.28(5H,m),1.02(3H,s),0.96(3H,s),0.94(3H,s)
Ex21	Ex1	ESI+:433
Ex22	Ex1	ESI+:415
Ex23	Ex1	ESI+:375
Ex24	Ex1	ESI+:403
Ex25	Ex1	ESI+:421
Ex26	Ex1	ESI+:395
Ex27	Ex1	ESI+:429
Ex28	Ex1	ESI+:361
Ex29	Ex1	ESI+:333
Ex30	Ex1	ESI+:443
Ex31	Ex31	ESI+:390 NMR(DMSO-d_6):7.56(1H,d,J=1.1Hz),4.67(2H,t,J=4.4Hz),3.85(1H,d,J=14.0Hz),3.78(1H,d,J=14.0Hz),3.25-3.08(2H,m),2.91-2.75(2H,m),2.74-2.67(1H,m),2.65(3H,s),2.07(1H,td,J=11.6,2.4Hz),1.95-1.85(3H,m),1.77-1.58(3H,m),1.51-1.44(2H,m),1.41-1.31(3H,m),0.95(3H,s),0.94(3H,s)
Ex31-1	Ex31	ESI+:390
Ex32	Ex31	ESI+:391 NMR($CDCl_3$):4.19(1H,d,J=14.0Hz),4,15(1H,d,J=14.0Hz),3.68-3.60(1H,m),3.56-3.48(1H,m),3.15-3.08(1H,m),3.04-2.92(2H,m),2.83(3H,s),2.62(1H,brs),2.47-2.36(1H,m),2.36-2.28(1H,m),2.07-1.97(3H,m),1.89(1H,brs),1.88-1.75(2H,m),1.74-1.62(1H,m),1.6-1.5(2H,m),1.43-1.32(2H,m),0.99(6H,s)
Ex32-1	Ex31	ESI+:391
Ex33	Ex33	ESI+:360
Ex34	Ex33	ESI+:360

[0220]

[Table 51]

No.	Ref	Data
Ex35	Ex33	ESI+:346
Ex36	Ex33	ESI+:346
Ex37	Ex33	ESI+:358
Ex38	Ex33	ESI+:358
Ex39	Ex33	ESI+:388
Ex40	Ex33	ESI+:388
Ex41	Ex33	ESI+:372
Ex42	Ex33	ESI+:344
Ex43	Ex33	ESI+:384
Ex44	Ex33	ESI+:386
Ex45	Ex33	ESI+:386
Ex46	Ex33	ESI+:418
Ex47	Ex33	ESI+:388 NMR(DMSO-d_6):10.1(1H,brs),7.55(1H,d,J=1.1Hz),4.83(2H,brs),4.08-3.58(2H,m),3.46-3.20(3H,m),2.93-2.82(1H,m),2.76(3H,s),1.96-1.82(4H,m),1.73-1.61(4H,m),1.53-1.45(2H,m),1.43-1.33(2H,m),1.30-1.16(3H,m),0.96(3H,s),0.95(3H,s)
Ex48	Ex33	ESI+:402
Ex49	Ex33	ESI+:360
Ex50	Ex33	ESI+:418
Ex51	Ex33	ESI+:392
Ex52	Ex52	ESI+:374 NMR(DMSO-d_6):10.41(1H,brs),7.57(1H,s),5.25-4.95(1H,brs),4.80(2H,brs),4.04-3.04(5H,m),2.94-2.80(1H,m),2.76(3H,s),2.08-1.87(4H,m),1.82-1.60(4H,m),1.54-1.44(2H,m),1.44-1.31(2H,m),0.96(3H,s),0.95(3H,s)
Ex53	Ex52	ESI+:330
Ex54	Ex52	ESI+:390
Ex55	Ex198	ESI+:394
Ex56	Ex198	ESI+:356
Ex57	Ex52	ESI+:346
Ex58	Ex52	ESI+:366
Ex59	Ex52	ESI+:330
Ex60	Ex52	ESI+:330
Ex61	Ex52	ESI+:408
Ex62	Ex52	ESI+:360

[0221]

[Table52]

No.	Ref	Data
Ex63	Ex52	ESI+:402
Ex64	Ex52	ESI+:332 NMR(DMSO-d_6):11.19(1H,brs),7.54(1H,d,J=1.1Hz),4.85(2H,brs),3.91(4H,brs),3.64-3.25(4H,brs),3.01-2.89(1H,m),2.75(3H,s),2.12-2.03(2H,m),1.86-1.76(2H,m),1.76-1.67(1H,m),1.55-1.35(4H,m),1.32-1.20(1H,m)
Ex65	Ex52	ESI+:359
Ex66	Ex52	ESI+:364
Ex67	Ex52	ESI+:365
Ex68	Ex52	ESI+:378
Ex69	Ex52	ESI+:379
Ex70	Ex52	ESI+:368
Ex71	Ex52	ESI+:368
Ex72	Ex52	ESI+:374
Ex73	Ex52	ESI+:374
Ex74	Ex52	ESI+:376
Ex75	Ex52	ESI+:356
Ex76	Ex52	ESI+:392
Ex77	Ex52	ESI+:384
Ex78	Ex52	ESI+:360
Ex79	Ex52	ESI+:388
Ex80	Ex52	ESI+:422
Ex81	Ex52	ESI+:346
Ex82	Ex52	ESI+:396
Ex83	Ex52	ESI+:396
Ex84	Ex52	ESI+:405
Ex85	Ex85	ESI+:376
Ex86	Pr8+Ex85	ESI+:371
Ex87	Ex85	ESI+:409
Ex88	Ex85	ESI+:419
Ex89	Ex85	ESI+:391
Ex90	Ex85	ESI+:391
Ex91	Ex85	ESI+:405
Ex92	Ex85	ESI+:445
Ex93	Ex85	ESI+:377

[0222]

[Table 53]

No.	Ref	Data
Ex94	Ex85	ESI+:431
Ex95	Ex85	ESI+:395
Ex96	Ex96	ESI+:388
Ex97	Pr8+Ex96	ESI+:396
Ex98	Ex96	ESI+:366
Ex99	Pr8+Ex96	ESI+:396
Ex100	Ex96	ESI+:422
Ex101	Ex96	ESI+:390
Ex102	Ex96	ESI+:390
Ex103	Ex96	ESI+:372
Ex104	Ex96	ESI+:404
Ex105	Ex105	ESI+:385
Ex106	Ex106	ESI+:346
Ex107	Ex107	ESI+:385
Ex108	Ex108	ESI+:406
Ex109	Ex109	ESI+:376
Ex110	Ex109	ESI+:376
Ex111	Ex109	ESI+:360
Ex112	Ex112	APCI/ESI+:344
Ex113	Ex112	ESI+:346
Ex114	Ex112	APCI/ESI+:330
Ex115	Ex112	ESI+:370
Ex116	Ex116	ESI+:348
Ex117	Ex116	ESI+:346
Ex118	Ex116	ESI+:374
Ex119	Ex116	ESI+:374
Ex120	Ex116	ESI+:388
Ex121	Ex116	ESI+:372
Ex122	Ex116	ESI+:373
Ex123	Ex116	ESI+:389
Ex124	Ex116	ESI+:415
Ex125	Ex116	ESI+:376
Ex126	Ex126	ESI+:372
Ex127	Ex126	ESI+:404
Ex128	Ex126	ESI+:391

[0223]

[Table 54]

No.	Ref	Data
Ex129	Pr33	ESI+:358
Ex130	Ex130	ESI+:344
Ex131	Ex130	ESI+:376
Ex132	Ex130	ESI+:360
Ex133	Ex130	ESI+:360
Ex134	Ex134	ESI+:346
Ex135	Ex134	ESI+:346
Ex136	Ex134	ESI+:360
Ex137	Ex134	ESI+:360
Ex138	Ex134	ESI+:332
Ex139	Ex134	ESI+:332
Ex140	Pr8+Pr34	ESI+:362
Ex141	Pr8+Pr34	ESI+:362
Ex142	Pr34	ESI+:402
Ex143	Pr34	ESI+:392
Ex144	Pr34	ESI+:392
Ex145	Pr34	ESI+:393
Ex146	Ex198	ESI+:402
Ex147	Ex198	ESI+:400
Ex148	Ex198	ESI+:348
Ex149	Ex198	ESI+:355
Ex150	Ex150	ESI+:374
Ex151	Ex150	ESI+:401
Ex152	Ex152	ESI+:360
Ex153	Ex153	ESI+:429
Ex154	Ex153	ESI+:413
Ex155	Ex155	ESI+:445
Ex156	Ex155	ESI+:429
Ex157	Ex155	ESI+:438
Ex158	Ex155	ESI+:446
Ex159	Ex155	ESI+:430
Ex160	Ex155	ESI+:455
Ex161	Ex161	ESI+:361
Ex162	Ex161	ESI+:361
Ex163	Ex163	ESI+:371
Ex164	Pr13+Ex52	ESI+:384

[0224]

[Table 55]

No.	Ref	Data
Ex165	Pr13+Ex52	ESI+:402
Ex166	Pr13+Ex52	ESI+:368
Ex167	Pr13+Ex52	ESI+:402
Ex168	Ex1	ESI+:388
Ex169	Ex1	ESI+:414
Ex170	Ex1	ESI+:332
Ex171	Ex33	ESI+:358
Ex172	Ex33	ESI+:372
Ex173	Ex33	ESI+:394
Ex174	Ex33	ESI+:388
Ex175	Ex33	ESI+:374
Ex176	Ex33	ESI+:416
Ex177	Ex33	ESI+:402
Ex178	Ex33	ESI+:432
Ex179	Ex33	ESI+:360
Ex180	Ex33	ESI+:388
Ex181	Ex33	ESI+:432
Ex182	Ex33	ESI+:344
Ex183	Ex52	ESI+:318
Ex184	Ex130	ESI+:378
Ex185	Ex52	ESI+:346
Ex186	Pr8+Ex85	ESI+:334
Ex187	Ex187	APCI/ESI+:386
Ex188	Ex188	ESI+:416
Ex189	Ex190	ESI+:348
Ex190	Ex190	ESI+:398
Ex191	Ex191	ESI+:436
Ex192	Ex191	ESI+:408
Ex193	Ex191	ESI+:450
Ex194	Ex191	ESI+:466
Ex195	Ex191	ESI+:360
Ex196	Ex196	ESI+:418
Ex197	Ex130	ESI+:290
Ex198	Ex198	ESI+:422
Ex199	Ex198	ESI+:422
Ex200	Ex198	ESI+:422

[0225]

[Table 56]

No.	Ref	Data
Ex201	Pr7-1	ESI+:291
Ex202	Ex187	ESI+:332
Ex203	Ex187	ESI+:398
Ex204	Ex187	ESI+:362
Ex205	Ex205	ESI+:436
Ex206	Ex206	ESI+:402
Ex207	Ex206	ESI+:414
Ex208	Ex206	ESI+:374
Ex209	Ex206	ESI+:372
Ex210	Ex206	ESI+:387 NMR(DMSO-d_6):7.11(1H,d,1.1Hz),3.74-3.67(2H,m),3.29-3.24(2H,m),2.94-2.84(1H,m),2.70(3H,s),2.46-2.40(2H,m),2.27-2.22(2H,m),2.20(3H,s),1.92-1.84(2H,m),1.71-1.58(2H,m),1.51-1.43(2H,m),1.40-1.29(2H,m),0.94(6H,s)
Ex211	Ex206	ESI+:388
Ex212	Ex206	ESI+:404
Ex213	Ex206	ESI+:401
Ex214	Ex206	ESI+:415
Ex215	Ex206	ESI+:413
Ex216	Ex206	ESI+:428
Ex217	Ex206	ESI+:413
Ex218	Ex206	ESI+:388
Ex219	Ex206	ESI+:388
Ex220	Ex206	ESI+:374
Ex221	Ex206	ESI+:374
Ex222	Ex206	ESI+:360
Ex223	Ex206	ESI+:389
Ex224	Ex206	ESI+:403
Ex225	Ex206	ESI+:417
Ex226	Ex206	ESI+:401
Ex227	Ex206	ESI+:403
Ex228	Ex206	ESI+:414
Ex229	Ex229	ESI+:436
Ex230	Ex229	ESI+:388
Ex231	Ex229	ESI+:402

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Industrial Applicability

[0226]

The compound of the present invention is a PAM of a $GABA_B$ receptor, and can be used as an agent for preventing and/or treating schizophrenia, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, Charcot-Marie-Tooth disease, or the like.

Furthermore, based on the knowledge obtained by the present invention, the PAM of the $GABA_B$ receptor can be used as a drug for preventing and/or treating schizophrenia, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, Charcot-Marie-Tooth disease, or the like.

[0227]

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0228]

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

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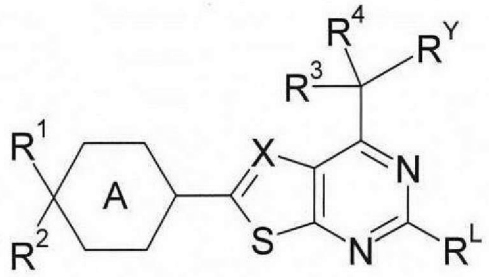
The claims defining the invention are as follows:

[Claim 1] A compound of the formula (I) or a salt thereof:

[Chem. 20]



(I)

(in the formula,

X is CH,

R^1 is lower alkyl,

R^2 is lower alkyl,

in which R^1 and R^2 may form a cycloalkane together with carbon atoms to which they are bonded,

R^3 is -H,

R^4 is -H,

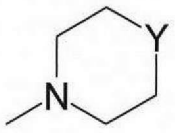
A ring is a cyclohexane ring,

R^Y is $-NR^AR^B$,

R^A and R^B form cyclic amino which may be substituted, together with a nitrogen atom to which they are bonded,

in which the cyclic amino is a group represented by the following formula (III):

[Chem. 21]



(III)

,

Y is NH, O, S, S $(=O)_2$, or CH_2, and

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R^L is lower alkyl).

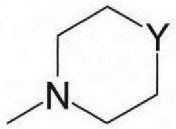
[Claim 2] The compound or salt thereof according to claim 1, wherein

R^Y is $-NR^AR^B$,

R^A and R^B form cyclic amino which may be substituted with R^0, together with a nitrogen atom to which they are bonded,

in which the cyclic amino is a group represented by the following formula (III):

[Chem. 22]



(III)

,

and

R^0 is a group selected from the following Group Z:

Group Z:

(1) =O,

(2) -OH,

(3) -O-lower alkyl,

(4) halogen,

(5) -CN,

(6) lower alkyl,

(7) halo-lower alkyl,

(8) lower alkylene-OH,

(9) lower alkylene-O-lower alkyl,

(10) -C(=O)-lower alkyl,

(11) -C(=O)-lower alkylene-OH,

(12) -C(=O)-lower alkylene-CN, and

(13) cycloalkyl.

[Claim 3] The compound or salt thereof according to claim 2, wherein the group selected from the Group Z is a group selected from:

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Group Z1:

(1) -OH,

(2) lower alkyl, and

(3) -C(=O)-lower alkylene-OH.

[Claim 4] The compound or salt thereof according to claim 3, wherein Y is O, S, or S $(=O)_2$.

[Claim 5] The compound or salt thereof according to claim 4, wherein R^L is CH_3.

[Claim 6] The compound or salt thereof according to claim 1, which is selected from the following compound group:

6-(4,4-dimethylcyclohexyl)-4-[(1,1-dioxo-1λ^6-thiomorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine,

trans-1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidine-3,4-diol,

1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidin-4-ol,

6-(4,4-dimethylcyclohexyl)-2-methyl-4-(thiomorpholin-4-ylmethyl)thieno[2,3-d]pyrimidine,

6-(4,4-dimethylcyclohexyl)-4-[(3,3-dimethylmorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine, and

1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-2,2-dimethylpiperidin-4-ol,

or a salt thereof.

[Claim 7] The compound or salt thereof according to claim 6, which is 6-(4,4-dimethylcyclohexyl)-4-[(1,1-dioxo-1λ^6-thiomorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine, or a salt thereof.

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[Claim 8] The compound or salt thereof according to claim 6, which is trans-1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidine-3,4-diol, or a salt thereof.

[Claim 9] The compound or salt thereof according to claim 6, which is 1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}piperidin-4-ol, or a salt thereof

[Claim 10] The compound or salt thereof according to claim 6, which is 6-(4,4-dimethylcyclohexyl)-2-methyl-4-(thiomorpholin-4-ylmethyl)thieno[2,3-d]pyrimidine, or a salt thereof.

[Claim 11] The compound or salt thereof according to claim 6, which is 6-(4,4-dimethylcyclohexyl)-4-[(3,3-dimethylmorpholin-4-yl)methyl]-2-methylthieno[2,3-d]pyrimidine, or a salt thereof.

[Claim 12] The compound or salt thereof according to claim 6, which is 1-{[6-(4,4-dimethylcyclohexyl)-2-methylthieno[2,3-d]pyrimidin-4-yl]methyl}-2,2-dimethylpiperidin-4-ol, or a salt thereof.

[Claim 13] A pharmaceutical composition comprising the compound or salt thereof according to any one of claims 1 to 12 and a pharmaceutically acceptable excipient.

[Claim 14] The pharmaceutical composition according to claim 13, which is a $GABA_B$ positive allosteric modulator.

[Claim 15] The pharmaceutical composition according to claim 13, which is a pharmaceutical composition for preventing or treating a disease selected from the group consisting of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, and Charcot-Marie-Tooth disease.

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[Claim 16] Use of the compound or salt thereof according to any one of claims 1 to 12 for the preparation of a pharmaceutical composition for preventing or treating a disease selected from the group consisting of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, and Charcot-Marie-Tooth disease.

[Claim 17] Use of the compound or salt thereof according to any one of claims 1 to 12 for preventing or treating a disease selected from the group consisting of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, and Charcot-Marie-Tooth disease.

[Claim 18] The compound or salt thereof according to any one of claims 1 to 12 for preventing or treating a disease selected from the group consisting of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, and Charcot-Marie-Tooth disease.

[Claim 19] A method for preventing or treating a disease selected from the group consisting of schizophrenia, CIAS, cognitive impairment, fragile X syndrome, autism spectrum disorder, spasticity, anxiety disorder, substance addiction, pain, fibromyalgia, and Charcot-Marie-Tooth disease, comprising administering to a subject in need thereof an effective amount of the compound or salt thereof according to any one of claims 1 to 12.