DESCRIPTION

3-PHENYLPYRAZOLO[5,1-*b*]THIAZOLE COMPOUND

Technical Field

[0001] The present invention relates to novel compounds having antagonism against corticotropin-releasing factor (hereunder, "CRF") receptor, salts thereof and medical use of the same.

Background Art

[0002] CRF is a neuropeptide consisting of 41 amino acids which is produced and secreted in the hypothalamus and promotes release of adrenocorticotropic hormone (ACTH) under stress, and it also functions in the brain as a neurotransmitter or neuromodulator, integrating electrophysiology, autonomic nerves and behavior in response to stress.

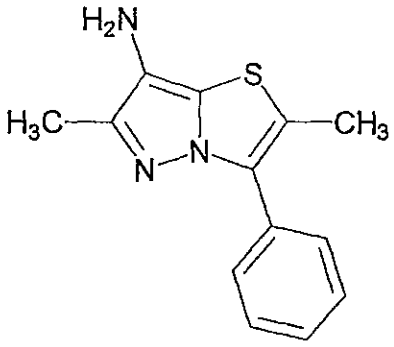
[0003] CRF receptors are of two subtypes, CRF1 receptors and CRF2 receptors, of which CRF1 receptors have been reported to be widely distributed in the cerebral cortex, cerebellum, olfactory bulb, pituitary gland, amygdaloid nucleus and elsewhere.

Numerous low molecular compounds having CRF receptor antagonism have been noted as potential therapeutic agents for a number of diseases including depression, anxiety and stress-related disorders. (See Non Patent Literature 1)

[0004] Disclosed compounds having CRF receptor antagonism include 2,6-dimethoxy-4-methoxymethylphenyl-containing compounds (see Patent Literature 1), but compounds having a pyrazolo[5,1-*b*]thiazole skeleton according to the present invention have been neither disclosed nor suggested.

[0005] The compound shown below has been disclosed as a compound having a pyrazolo[5,1-*b*]thiazole skeleton, but its use is for colorimetry. (See Example 16 of Patent Literature 2)

[Chemical Formula 1]



Citation List

[Patent Literature]

[0006]

[Patent Literature 1] U.S. Patent Application Publication No. 2004/0224974

[Patent Literature 2] U.S. Patent No. 5234818

[Non Patent Literature]

[0007]

[Non Patent Literature 1] Drugs of the Future, 24:1089-1098(1999)

Summary of Invention

Technical Problem

[0008] Absolutely no 3-phenylpyrazolo[5,1-*b*]thiazole compounds having superior CRF receptor antagonism are known. Furthermore, although compounds having CRF receptor antagonism have been reported, they have not necessarily been adequate in terms of exhibiting superior CRF receptor antagonism, and in terms of having sufficient pharmacological activity, safety and pharmacokinetic properties as medicaments.

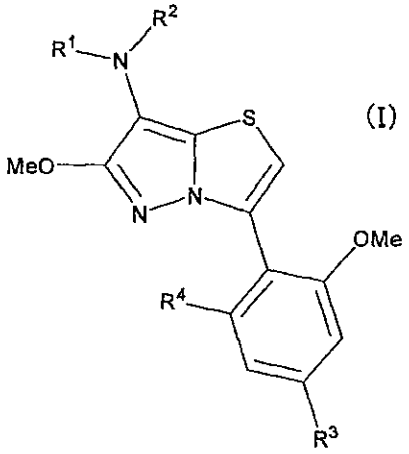
Solution to Problem

[0009] As a result of diligent research in light of the current circumstances, the present inventors have discovered novel compounds that are excellent CRF receptor antagonists with sufficient pharmacological activity, safety and pharmacokinetic properties, which are therefore useful as prophylactic or therapeutic agents for depression, anxiety, irritable bowel syndrome and the like.

[0010] Specifically, the invention relates to the following.

<1> A compound represented by the following formula (I) or salt thereof.

[Chemical Formula 2]



(I)

wherein

R^1 represents the formula $-A^{11}-A^{12}$;

R^2 represents tetrahydrofurylmethyl, tetrahydropyranylmethyl or tetrahydropyranyl;

A^{11} represents a single bond, methylene group or 1,2-ethylene;

A^{12} represents C1-6 alkyl or C3-6 cycloalkyl, or C3-6 cycloalkyl having methyl;

R^3 represents methoxy, cyano, cyclobutyloxymethyl, methoxymethyl or ethoxymethyl; and

R^4 represents methoxy group or chlorine.

<2> A compound or salt thereof according to <1> above, wherein R^2 is tetrahydropyran-4-yl, tetrahydropyran-3-yl, (tetrahydropyran-4-yl)methyl or (tetrahydrofuran-3-yl)methyl.

<3> A compound or salt thereof according to <1> or <2> above, wherein R^1 is n-propyl, n-butyl, n-pentyl, cyclopropylmethyl, cyclobutylmethyl, 2-(cyclopropyl)ethyl or (2-methylcyclopropyl)methyl.

<4> A pharmaceutical composition comprising a compound or salt thereof according to any one of <1> to <3> above as an active ingredient.

<5> A pharmaceutical composition according to <4> above, which is a CRF1 receptor antagonist.

<6> A therapeutic or prophylactic agent for a disease for which CRF1 receptor antagonist is effective, comprising a compound or salt thereof according to any one of <1> to <3> above.

<7> A therapeutic or prophylactic agent for depression, depressive symptoms, anxiety, irritable bowel syndrome, sleep disorder, insomnia, alcohol dependence, alcohol withdrawal symptoms, drug dependence, drug withdrawal symptoms, stress-related gastrointestinal dysfunction, anorexia nervosa, eating disorder, postoperative ileus, ischemic neuropathy, apoplexy, excitotoxic neuropathy, convulsion, epilepsy, hypertension, schizophrenia, bipolar disorder or dementia, which comprises a compound or salt thereof according to any one of <1> to <3> above.

<8> A therapeutic or prophylactic agent for depression, depressive symptoms, anxiety or irritable bowel syndrome, comprising a compound or salt thereof according to any one of <1> to <3> above.

<9> A method for treatment or prevention of depression, depressive symptoms, anxiety, irritable bowel syndrome, sleep disorder, insomnia, alcohol dependence, alcohol withdrawal symptoms, drug dependence, drug withdrawal symptoms, stress-related gastrointestinal dysfunction, anorexia nervosa, eating disorder, postoperative ileus, ischemic neuropathy, apoplexy, excitotoxic neuropathy, convulsion, epilepsy, hypertension, schizophrenia, bipolar disorder or dementia, comprising administering to a patient, a compound or salt thereof according to any one of <1> to <3> above.

<10> A method for treatment or prevention of depression, depressive symptoms, anxiety or irritable bowel syndrome, comprising administering to a patient, a compound or salt thereof according to any one of <1> to <3> above.

<11> A compound or salt thereof according to any one of <1> to <3> above for treatment or prevention of depression, depressive symptoms, anxiety, irritable bowel syndrome, sleep disorder, insomnia, alcohol dependence, alcohol withdrawal symptoms, drug dependence, drug withdrawal symptoms, stress-related gastrointestinal dysfunction, anorexia nervosa, eating disorder, postoperative ileus, ischemic neuropathy, apoplexy, excitotoxic neuropathy, convulsion, epilepsy, hypertension, schizophrenia, bipolar disorder or dementia.

<12> A compound or salt thereof according to any one of <1> to <3> above for treatment or prevention of depression, depressive symptoms, anxiety or irritable bowel syndrome.

<13> Use of a compound or salt thereof according to any one of <1> to <3> above

for the manufacture of a therapeutic or prophylactic agent for depression, depressive symptoms, anxiety, irritable bowel syndrome, sleep disorder, insomnia, alcohol dependence, alcohol withdrawal symptoms, drug dependence, drug withdrawal symptoms, stress-related gastrointestinal dysfunction, anorexia nervosa, eating disorder, postoperative ileus, ischemic neuropathy, apoplexy, excitotoxic neuropathy, convulsion, epilepsy, hypertension, schizophrenia, bipolar disorder or dementia.

<14> Use of a compound or salt thereof according to any one of <1> to <3> above for the manufacture of a therapeutic or prophylactic agent for depression, depressive symptoms, anxiety or irritable bowel syndrome.

<15-1> *N*-Butyl-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-2> *N*-Butyl-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-3> *N*-(2-Cyclopropylethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-4> *N*-(Cyclobutylmethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-5> *N*-(Cyclopropylmethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-6> 3-[4-(Ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-7> *N*-(Cyclobutylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-8> 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-pentyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-9> *N*-(Cyclopropylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-10> 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-11> *N*-(Cyclopropylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-12> 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-[(2-methylcyclopropyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-13> 3-[2-Chloro-6-methoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-14> 4-{7-[(Cyclopropylmethyl)(tetrahydrofuran-3-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile or salt thereof.

<15-15> 4-{7-[(Cyclopropylmethyl)(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile or salt thereof.

<15-16> *N*-(Cyclopropylmethyl)-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-3-(2,4,6-trimethoxyphenyl)-pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

<15-17> 3-{4-[(Cyclobutyloxy)methyl]-2,6-dimethoxyphenyl}-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

Advantageous Effect of Invention

[0011] CRF receptor antagonists have been reported to be effective for a wide range of diseases, which are listed below.

(1) Depression, depressive symptoms, anxiety

CRF1 receptor antagonist R121919 is effective for ameliorating depression, depressive symptoms, anxiety and the like. (Journal of Psychiatric Research, 34:171-181(2000))

CRF1 receptor antagonist R121919 exhibits an anti-anxiety action in rats. (European Journal of Neuroscience, 13:373-380(2001))

CRF1 receptor antagonist CP-154526 exhibits anti-depressant and anti-anxiety actions in rats. (European Journal of Pharmacology, 492:195-201(2004))

(2) Irritable bowel syndrome (IBS)

CRF1 receptor antagonist α-helical CRF(9-41) inhibits colon intestinal hyperkinesis in IBS patients and reduces abdominal pain and anxiety. (Gut 2004; 53:958-964)

(3) Sleep disorder, insomnia

CRF1 receptor antagonist R121919 inhibits stress-related sleep disorder particularly in high-anxiety rats. (Journal of Psychiatric Research, 36:197-208(2002))

(4) Alcohol dependence, alcohol withdrawal symptoms, drug dependence, drug withdrawal symptoms

CRF1 receptor antagonist CP-154526 inhibits recurrence of stress-elicited alcohol-seeking behavior in rats. (Psychopharmacology, 150:317-324(2000))

CRF1 receptor antagonist α-helical CRF(9-41) inhibits anxiety behavior in ethanol withdrawal rats. (Brain Research, 605:25-32(1993))

CRF1 receptor antagonist CP-154526 inhibits recurrence of stress-elicited drug (heroin, cocaine)-seeking behavior in rats. (Psychopharmacology, 137:184-190(1998))

Pretreatment with CRF1 receptor antagonist CP-154526 inhibits naltrexone-induced morphine withdrawal symptoms. (Journal of Neurochemistry, 74:199-208(2000))

(5) Stress-related gastrointestinal dysfunction

CRF1 receptor antagonist NBI-27914 inhibits water avoidance stress-related rat catharsis. (Brain Research, 893:29-35(2001))

(6) Anorexia nervosa, eating disorder

CRF1 receptor antagonists α-helical CRF(9-41) and CRA1000 inhibit stress-related reduction in food intake. (Brain Research, 823:221-225(1999))

(7) Postoperative ileus

CRF1 receptor antagonist CP-154526 ameliorates gastric emptying retardation following surgery. (Gastroenterology, 125:654-659(2003))

(8) Dementia, Alzheimer-type senile dementia, multi-infarct dementia, senile dementia

CRF1 receptor antagonist CP-154526 inhibits learning disturbance following acute stress. (Behavioural Brain Research, 138:207-213(2003))

CRF1 receptor antagonist α-helical CRF(9-41) suppresses stress-related

increase in intracerebral amyloid-β. (Proceedings of the National Academy of Sciences of the United States of America, 104:10673-10678(2007))

CRF1 receptor antagonist NBI27914 inhibits increased levels of Aβ and Aβ plaque deposition induced by stress in Tg2576 mice (Journal of Neurochemistry, 108: 165-175 (2009))

CRF1 receptor antagonist antalarmin inhibits stress-induced hippocampal tau phosphorylation (Journal of Neuroscience, 27 (24): 6552-6562 (2007))

(9) Ischemic neuropathy, apoplexy

CRF1 receptor antagonist α-helical CRF(9-41) inhibits ischemic and excitotoxic encephalopathy. (Brain Research, 656:405-408(1994))

(10) Excitotoxic neuropathy

CRF1 receptor antagonist Asressin inhibits kainic acid-induced excitotoxic neuropathy. (Brain Research, 744:166-170(1997))

(11) Convulsion, epilepsy

CRF1 receptor antagonist NBI27914 inhibits limbic system seizure (convulsion and epilepsy induced by CRF administration). (Brain Research, 770:89-95(1997))

(12) Hypertension

CRF1 receptor antagonist Antalarmin inhibits hypertension induced by intraventricular administration of CRF. (Brain Research, 881:204-207(2000))

[0012] The compounds and salts thereof according to the invention have excellent CRF receptor antagonism, as evidenced by the activity data in the Pharmacological Test Examples described below. Thus, based on the aforementioned publications demonstrating a correlation between CRF receptor antagonism and effects of treating or preventing diseases, the compounds or salts thereof according to the invention are useful for treatment or prevention of diseases associated with CRF and/or CRF receptors, and are particularly useful as therapeutic or prophylactic agents for depression, depressive symptoms, anxiety, irritable bowel syndrome, sleep disorder, insomnia, alcohol dependence, alcohol withdrawal symptoms, drug dependence, drug withdrawal symptoms, stress-related gastrointestinal dysfunction, anorexia nervosa, eating disorder, postoperative ileus, ischemic neuropathy, apoplexy, excitotoxic neuropathy, convulsion, epilepsy, hypertension, schizophrenia, bipolar disorder or dementia.

Description of Embodiments

[0013] The present invention will now be explained in detail.

[0014] Throughout the present specification, the structural formulas for the compounds will show only one specific isomer for convenience, but the invention includes all isomers such as geometric isomers, optical isomers, stereoisomers and tautomers implied by the compound structures, as well as their isomer mixtures, and the compounds may therefore be any of the isomers or mixtures thereof in any desired proportion, without being limited to the formulas that are shown for convenience. Thus, for example, the compounds of the invention may exist as optically active forms or racemic mixtures, all of which are included without limitations according to the invention, and whether racemic mixtures or optically active forms, they may be used as mixtures with the optically active forms in any desired proportion.

[0015] Polymorphic crystals may also exist, and there may be used any crystal form or a mixture thereof without any restrictions, as well as amorphous forms, and the compounds of the invention also include both anhydrate and solvate (especially hydrate). The invention further encompasses metabolites of compound (I) according to the invention, that are produced by metabolism (oxidation, reduction, hydrolysis, conjugation and the like) in the body. The invention still further encompasses compounds that yield compound (I) according to the invention by metabolism (oxidation, reduction, hydrolysis, conjugation and the like) in the body (so-called prodrugs).

[0016] The meanings of the terms and symbols used throughout the present specification will now be explained, followed by a more detailed description of the invention.

[0017] The term "C1-6 alkyl" used throughout the present specification refers to C1-6 straight-chain or branched alkyl groups, and as specific examples there may be mentioned methyl, ethyl, 1-propyl (*n*-propyl), 2-propyl (*i*-propyl), 2-methyl-1-propyl (*i*-butyl), 2-methyl-2-propyl (*tert*-butyl), 1-butyl (*n*-butyl), 2-butyl (*s*-butyl), 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2,2-dimethyl-1-propyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2-methyl-3-pentyl, 3-methyl-3-pentyl, 2,3-dimethyl-1-

butyl, 3,3-dimethyl-1-butyl, 2,2-dimethyl-1-butyl, 2-ethyl-1-butyl, 3,3-dimethyl-2-butyl and 2,3-dimethyl-2-butyl.

[0018] The term "C3-6 cycloalkyl" used throughout the present specification refers to C3-6 monocyclic saturated aliphatic hydrocarbon groups, and as specific examples there may be mentioned cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0019] As specific examples of the "C3-6 cycloalkyl having methyl" referred to throughout the present specification there may be mentioned 2-methylcyclobutyl, 3-methylcyclobutyl and 2-methylcyclopropyl, among which 2-methylcyclopropyl is preferred.

[0020] As specific examples of "tetrahydropyranyl" referred to throughout the present specification there may be mentioned tetrahydropyran-4-yl and tetrahydropyran-3-yl, with tetrahydropyran-4-yl being preferred.

[0021] As specific examples of "tetrahydropyranylmethyl" referred to throughout the present specification there may be mentioned (tetrahydropyran-4-yl)methyl, (tetrahydropyran-3-yl)methyl and (tetrahydropyran-2-yl)methyl, among which (tetrahydropyran-4-yl)methyl is preferred.

[0022] As specific examples of "tetrahydrofurylmethyl" referred to throughout the present specification there may be mentioned (tetrahydrofuran-3-yl)methyl and (tetrahydrofuran-2-yl)methyl, with (tetrahydrofuran-3-yl)methyl being preferred.

[0023] The term "anxiety" used in the present specification refers not only to anxiety in the strict sense, but also to conditions within the general concept of anxiety, such as generalized anxiety disorder, panic disorder, phobia, obsessive compulsive disorder and post-traumatic stress disorder, as well as diseases closely related to anxiety.

[0024] The term "dementia" used in the present specification refers not only to dementia in the strict sense, but also conditions within the general concept of dementia, such as Alzheimer-type senile dementia, multi-infarct dementia and senile dementia, as well as diseases closely related to dementia.

[0025] A "salt" used in the present specification is not particularly restricted so long as it is formed with the compound of the invention, although it is preferably a pharmacologically acceptable salt, and as specific examples there may be mentioned inorganic acid salts, organic acid salts and acidic amino acid salts.

[0026] A "salt" used in the present specification, unless otherwise specified, may form a salt with an appropriate ratio, and the number of the acid molecule against one molecule of the compound is not particularly restricted, but preferably approximately 0.1 to approximately 5 molecules of the acid exist against one molecule of the compound, more preferably approximately 0.5 to approximately 2 molecules of the acid exist against one molecule of the compound, and even more preferably approximately 0.5, approximately 1 or approximately 2 molecules of the acid exist against one molecule of the compound.

[0027] As preferred examples of inorganic acid salts there may be mentioned hydrochloride, hydrobromide, sulfate, nitrate and phosphate, and as preferred examples of organic acid salts there may be mentioned acetate, succinate, fumarate, malate, tartrate, citrate, lactate, stearate, benzoate, methanesulfonate and *p*-toluenesulfonate.

[0028] As preferred examples of acidic amino acid salts there may be mentioned aspartate and glutamate.

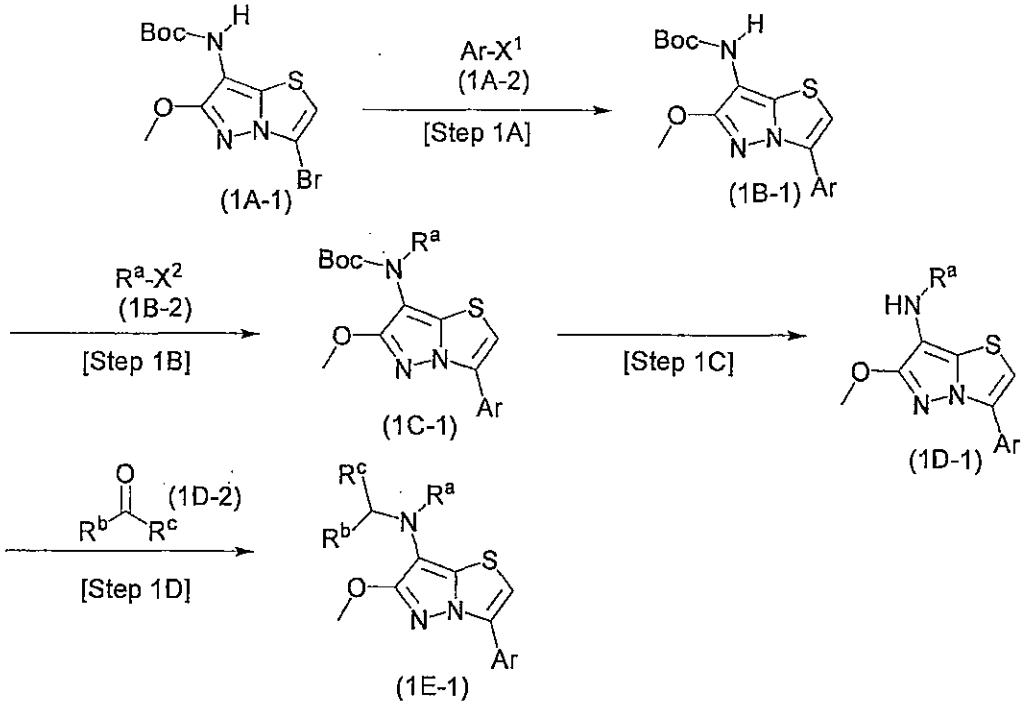
[0029] (General production schemes)

General production schemes for compounds according to the invention will be outlined below, although they are not intended to be restrictive. The starting compounds and reagents used in the general production schemes for compounds of the invention may also form salts or solvates (especially hydrates).

[0030] The compounds represented by general formula (I) of the invention can be produced by the following production schemes.

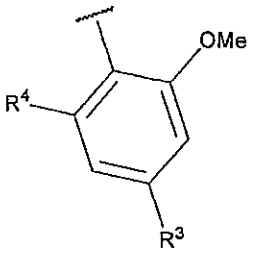
[0031] Production Scheme 1

[Chemical Formula 3]



wherein Ar corresponds to the group represented by the formula:

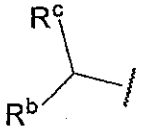
[Chemical Formula 4]



in compound (I) described above;

R^a and the group represented by the formula:

[Chemical Formula 5]



each independently corresponds to R^1 or R^2 above;

X^1 represents $B(OH)_2$ or the like;

X^2 represents a leaving group such as iodine, bromine, chlorine, methanesulfonyloxy or *p*-toluenesulfonyloxy; and

Boc represents *tert*-butoxycarbonyl.

[0032] Step 1A

This is a step of reacting compound (1A-1) and compound (1A-2) in a solvent in the presence of a base and a palladium catalyst to produce compound (1B-1).

The step can be carried out with reference to the reaction conditions described in WO 04/037822 (step 5-E of Production Process 5, Example 47) and in (2f) of Example 2 below and the like.

The compounds represented by general formula (1A-1) can be produced according to (2e) of Example 2 and the like.

For a compound represented by general formula (1A-2) there may be used a compound that can be produced under the reaction conditions described in WO 04/037822 (Production Examples 29 and 33) and in Production Examples 1C(3) and 2C(6) and Examples 16(b) and 17(d) below and the like. For a compound represented by general formula (1A-2) there may be used any commercially available compound, or a compound that can be easily produced by a person skilled in the art from a commercially available compound.

The reaction may be carried out under a stream or in an atmosphere of an inert gas such as nitrogen or argon.

The solvent used for the reaction is not particularly restricted so long as it dissolves the starting materials to some extent and does not interfere with the reaction, and examples include alcohol solvents such as methanol, ethanol and *n*-butanol, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, cyclopentyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether, dicyclopentyl ether, 1,2-dimethoxyethane and 1,4-dioxane, aromatic hydrocarbon solvents such as benzene, toluene, xylene and mesitylene, amide solvents such as *N,N*-dimethylformamide, aliphatic hydrocarbon solvents such as heptane and hexane, or 1-methyl-2-pyrrolidinone, water, and mixtures thereof, among which preferred solvents are water, alcohol solvents, aromatic hydrocarbon solvents, ether solvents and mixtures thereof, and more preferred solvents are a mixed solvent of ethanol and toluene, or a mixed solvent of 1,2-dimethoxymethane and water.

The base used in this step is not particularly restricted and will differ depending on the starting material and solvent used, but examples include inorganic bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide,

barium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, cesium carbonate, cesium fluoride and potassium fluoride, cyclic bases such as imidazole and pyridine and organic amines such as triethylamine and *N,N*-diisopropylethylamine, among which sodium carbonate and potassium carbonate are preferred.

The palladium catalyst is not particularly restricted so long as it does not interfere with the reaction, and will differ depending on the starting material and solvent used, but as preferred examples there may be mentioned tetrakis(triphenylphosphine)palladium(0), palladium(II) acetate/triphenylphosphine, palladium(II) acetate/2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, palladium(II) chloride, tris(dibenzylideneacetone)dipalladium(0)/tri-*tert*-butylphosphine and dichloro[1,1'-bis(diphenylphosphine)-ferrocene]palladium(0).

The reaction temperature will generally differ depending on the starting materials, solvent and other reagents used in the reaction, but it is preferably between 0°C and the reflux temperature of the solvent (as the reactor internal temperature), and more preferably 60°C-100°C.

The reaction time will also, in general, differ depending on the starting materials, solvent and other reagents used in the reaction, and on the reaction temperature, but it is preferably 1-48 hours and more preferably 1-6 hours at the aforementioned reaction temperature after addition of the reagents.

Compound (1A-2) may be used at 1-5 molar equivalents and preferably 1-3 molar equivalents with respect to compound (1A-1).

The aforementioned base may be used at 1-10 molar equivalents and preferably 2-5 molar equivalents with respect to compound (1A-1).

The palladium catalyst may be used at 0.01-1 molar equivalents and preferably 0.05-0.1 molar equivalents with respect to compound (1A-1).

[0033] Step 1B

This is a step of reacting compound (1B-1) and compound (1B-2) in a solvent in the presence of a base to produce compound (1C-1).

The step can be carried out with reference to the reaction conditions described in WO 04/037822 (step 5-A of Production Process 5, and Production Example 24) and in (2g) of Example 2 below and the like.

The reaction may be carried out under a stream or in an atmosphere of an

inert gas such as nitrogen or argon.

Compound (1B-2) may be a compound that can be produced under the reaction conditions described in Production Example 1B below and the like. Compound (1B-2) may be a commercially available compound, or a compound that can be easily produced by a person skilled in the art from a commercially available compound.

The solvent used for this reaction is not particularly restricted so long as it dissolves the starting materials to some degree and does not interfere with the reaction, and for example, there may be used nitrile solvents such as acetonitrile, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, cyclopentyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether and dicyclopentyl ether, aromatic hydrocarbon solvents such as benzene and toluene, amide solvents such as *N,N*-dimethylformamide, aliphatic hydrocarbon solvents such as heptane and hexane, dimethyl sulfoxide, or mixtures thereof, among which *N,N*-dimethylformamide and dimethyl sulfoxide are preferred.

The base used for this step is not particularly restricted and will differ depending on the starting material and solvent used, but as examples there may be mentioned inorganic bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and cesium carbonate, organometallic bases such as potassium-*tert*-butoxide, butyllithium, methyllithium, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide and potassium bis(trimethylsilyl)amide, hydride bases such as lithium hydride, sodium hydride and potassium hydride, cyclic bases such as imidazole, pyridine and 4-dimethylaminopyridine, and organic amines such as triethylamine and *N,N*-diisopropylethylamine, among which sodium hydride and sodium hydroxide are preferred.

The reaction temperature will generally differ depending on the starting materials, solvent and other reagents used in the reaction, but it is preferably 0°C-80°C (as the reactor internal temperature).

The reaction time will generally differ depending on the starting materials, the solvent and the other reagents used in the reaction, and on the reaction temperature, but preferably stirring is carried out for 1-8 hours at the

aforementioned reaction temperature after addition of the reagents.

Compound (1B-2) may be used at 1-5 moles with respect to compound (1B-1).

The base may be used at 1-5 molar equivalents and preferably 1.5 molar equivalents with respect to compound (1B-1).

[0034] Step 1C

This is a step of acid treatment of compound (1C-1) to produce compound (1D-1).

The step can be carried out with reference to the reaction conditions described in WO 04/037822 (step 5-B of Production Process 5, and Production Example 24) and in (2g) of Example 2 below and the like.

This step can be carried out in the presence or in the absence of a solvent, and when a solvent is used, the solvent used for the reaction is not particularly restricted so long as it can dissolve the starting materials to some extent and does not interfere with the reaction, and examples include ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, cyclopentyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether, dicyclopentyl ether and 1,4-dioxane, aromatic hydrocarbon solvents such as benzene and toluene, aliphatic hydrocarbon solvents such as heptane and hexane, ethyl acetate, halogen solvents such as dichloromethane, acetonitrile, and mixtures thereof, with dichloromethane being preferred.

The acid used in this step may be hydrochloric acid, sulfuric acid, trifluoroacetic acid or the like, with trifluoroacetic acid being preferred.

The reaction temperature will generally differ depending on the starting materials, solvent and other reagents used in the reaction, but it is preferably 0°C-40°C (as the reactor internal temperature).

The reaction time will also differ in most cases depending on the starting materials, the solvent and the other reagents used in the reaction, and on the reaction temperature, but preferably stirring is carried out for 1-8 hours at the aforementioned reaction temperature after addition of the reagents.

The acid may be used in an amount of 1 mol or more with respect to compound (1C-1), and a large excess of acid may also be used as the reaction solvent.

The product of step 1B and step 1C may be used as starting material for the subsequent step without any special purification, with only a procedure of simple treatment of the reaction mixture and distilling off the solvent, similar to (2g) in Example 2 described below.

[0035] Step 1D

This is a step of reacting compound (1D-1) and compound (1D-2) in a solvent, in the presence of a reducing agent and in the presence or in the absence of an acid, to produce compound (1E-1).

The step can be carried out with reference to the reaction conditions described in WO 04/037822 (step 5-C of Production Process 5, and Production Example 24) and in (2g) of Example 2 and the like.

The reaction may be carried out under a stream or in an atmosphere of an inert gas such as nitrogen or argon.

Compound (1D-2) may be an aldehyde compound or ketone compound as defined above, and there may be used a compound that can be produced under the reaction conditions described in Production Example 1A below and the like, a commercially available compound, or a compound that can be easily produced by a person skilled in the art from a commercially available compound using ordinary methods.

The solvent used for this reaction is not particularly restricted so long as it dissolves the starting materials to some degree and does not interfere with the reaction, and as examples there may be mentioned alcohol solvents such as methanol and ethanol, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, cyclopentyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether and dicyclopentyl ether or acetic acid and the like, any of which may be used alone or as mixed solvents.

The reducing agent may be a reducing agent that is commonly used for reductive amination between carbonyl compounds and amine compounds and is not particularly restricted for this reaction, and α-picolineborane, sodium triacetoxyborohydride and sodium borohydride may be mentioned as examples.

The acid used for the reaction may be trifluoroacetic acid, acetic acid and the like.

The reaction temperature will generally differ depending on the starting

materials, solvent and other reagents used in the reaction, but it is preferably between 0°C and the reflux temperature of the solvent (as the reactor internal temperature), and is more preferably room temperature.

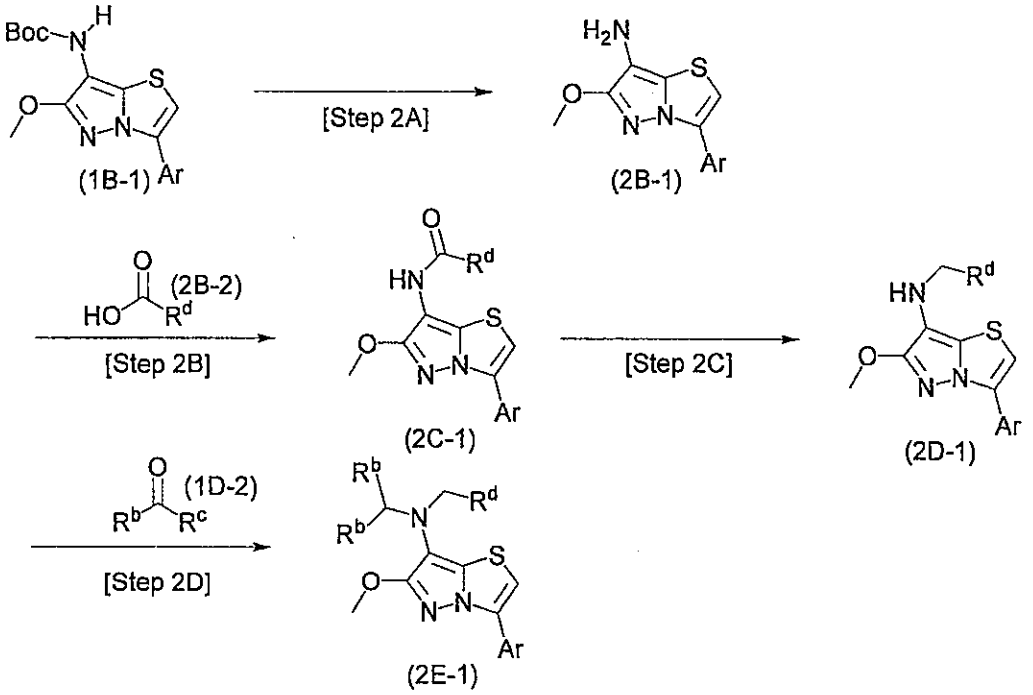
The reaction time will also, in general, differ depending on the starting materials, solvent and other reagents used in the reaction, and on the reaction temperature, but it is preferably 1-48 hours and more preferably 1-6 hours at the aforementioned reaction temperature after addition of the reagents.

The reducing agent may be used at 0.5-3 molar equivalents and preferably 1-2 molar equivalents with respect to compound (1D-1).

Compound (1D-2) may be used at 1-5 molar equivalents and preferably 1-2 molar equivalents with respect to compound (1D-1).

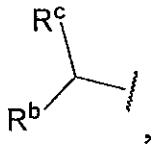
[0036] Production Scheme 2

[Chemical Formula 6]



wherein Ar is a group represented by the formula:

[Chemical Formula 7]



,

Boc has the same definition as above, and

the group represented by R^d-CH_2- corresponds to R^1 or R^2.

[0037] Step 2A

This is a step of acid treatment of compound (1B-1) to produce compound (2B-1).

This step may be carried out under the reaction conditions described for step 1C of Production Scheme 1, or with reference to the reaction conditions described in (12a) of Example 12 below and the like.

The solvent used for the reaction is not particularly restricted so long as it dissolves the starting materials to some extent and does not interfere with the reaction, and for example, ethyl acetate, water or a mixed solvent thereof may be used.

The acid used in this step may be hydrochloric acid, sulfuric acid, trifluoroacetic acid and the like, but it is preferably a solution of hydrochloric acid in ethyl acetate, or trifluoroacetic acid.

The reaction temperature will generally differ depending on the starting materials, solvent and other reagents used in the reaction, but it is preferably 0°C-40°C.

The reaction time will also, in general, differ depending on the starting materials, solvent and other reagents used in the reaction, and on the reaction temperature, but it is preferably 1-48 hours and more preferably 1-6 hours at the aforementioned reaction temperature after addition of the reagents.

The acid may be used in an amount of 1 mol or more with respect to compound (1B-1), and a large excess of acid may also be used as the reaction solvent.

[0038] Step 2B

This is a step of reacting compound (2B-1) and compound (2B-2) in a solvent in the presence of a condensation agent to produce compound (2C-1).

This step may be carried out with reference to the reaction conditions described in (12b) of Example 12 below and the like.

As compounds represented by general formula (2B-2), there may be used a commercially available compound, or a compound that can be easily produced by a person skilled in the art from a commercially available compound.

The reaction may be carried out under a stream or in an atmosphere of an

inert gas such as nitrogen or argon.

The solvent used for the reaction is not particularly restricted so long as it can dissolve the starting materials to some extent and does not interfere with the reaction, and examples include ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, cyclopentyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether, dicyclopentyl ether, 1,2-dimethoxyethane and 1,4-dioxane, amide solvents such as *N,N*-dimethylformamide, and a mixed solvent thereof.

The condensation agent for this step will differ depending on the starting materials and the solvent used and is not particularly restricted, and examples include water-soluble carbodiimide (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), 1-hydroxybenzotriazole, and a mixture thereof.

The reaction temperature will generally differ depending on the starting materials, solvent and other reagents used in the reaction, but it is preferably 0°C-40°C.

The reaction time will also differ in most cases depending on the starting materials, the solvent and the other reagents used in the reaction, and on the reaction temperature, but it is preferably 1-48 hours at the aforementioned temperature after addition of the reagents.

Compound (2B-2) may be used at 1-5 molar equivalents and preferably 1-1.5 molar equivalents with respect to compound (2B-1).

The condensation agent may be used at 1-10 molar equivalents with respect to compound (2B-1).

[0039] Step 2C

This is a step of reducing compound (2C-1) in a solvent in the presence of a reducing agent to produce compound (2D-1).

The step may be carried out with reference to the reaction conditions described in (12c) of Example 12 below and the like.

The reaction may be carried out under a stream or in an atmosphere of an inert gas such as nitrogen or argon.

The solvent used for the reaction is not particularly restricted so long as it can dissolve the starting materials to some extent and does not interfere with the

reaction, and examples include ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, cyclopentyl methyl ether, diethyl ether, diisopropyl ether, dibutyl ether, dicyclopentyl ether, 1,2-dimethoxyethane and 1,4-dioxane, among which tetrahydrofuran is preferred.

The reducing agent for this step will differ depending on the starting materials and the solvent used and is not particularly restricted, and examples include borane and a solution of borane in tetrahydrofuran.

The reaction temperature will generally differ depending on the starting materials, solvent and other reagents used in the reaction, but it is preferably from 0°C to the reflux temperature of the solvent (as the reactor internal temperature).

The reaction time will also differ in most cases depending on the starting materials, the solvent and the other reagents used in the reaction, and on the reaction temperature, but it is preferably 1-24 hours at the aforementioned temperature after addition of the reagents.

The reducing agent may be used at 1-10 molar equivalents and preferably 2-5 molar equivalents with respect to compound (2C-1).

The product of step 2C may be used as starting material for the subsequent step without any special purification, with only a procedure of simple treatment of the reaction solution and distilling off the solvent, similar to (12c) in Example 12 described below.

[0040] Step 2D

This is a step in which compound (2D-1) and compound (1D-2) are reacted to obtain compound (2E-1).

The reaction conditions for this step may be the same conditions by the same procedure as in step 1D of Production Scheme 1.

Upon completion of the reaction in each step of the processes described above, the target compound of each step may be recovered from the reaction mixture by an ordinary method.

[0041] [Reaction treatment method]

When the reaction mixture is a liquid, for example, the reaction mixture is returned to room temperature or cooled on ice as desired, and neutralized with an appropriate acid, alkali, oxidizing agent or reducing agent, followed by addition of water and an organic solvent that is immiscible therewith and does not react with

the target compound, such as ethyl acetate. After thoroughly shaking the mixture, it is allowed to stand for separation and the layer of the resulting bilayer that contains the target compound is separated. Next, a solvent that is immiscible with the obtained layer and does not react with the target compound is added, and then the layer containing the target compound is washed and separated. When the layer is an organic layer, it may be dried using a desiccant such as anhydrous magnesium sulfate or anhydrous sodium sulfate, and the solvent distilled off to obtain the target compound. When the layer is an aqueous layer, it may be electrically desalted and then freeze-dried to obtain the target compound.

[0042] When the entire reaction mixture is a liquid, it may be possible to recover the target compound simply by distilling off the components other than the target compound (for example, solvent, reagents, etc.) at ordinary pressure or under reduced pressure.

[0043] When the target compound precipitates alone as a solid, or when the entire reaction mixture is a liquid and the target compound precipitates alone as a solid during the collecting process, the target compound may be first collected by a filtration method, the collected target compound washed with a suitable organic or inorganic solvent and drying carried out as suitable to obtain the target compound.

[0044] On the other hand, when the reagents or catalyst are the only solids present, or when the reagents or catalyst alone precipitate as solid during treatment of the reaction mixture, with the target compound remaining dissolved in solution, the reagents or catalyst may be first removed by a filtration method, the removed reagents or catalyst washed with a suitable organic or inorganic solvent, and the obtained wash combined with the mother liquor to obtain a liquid mixture, which may then be treated in the same manner as in the case that the entire reaction mixture is a liquid, in order to obtain the target compound.

[0045] The reaction mixture may be used directly for subsequent steps without isolation of the target compound in cases where components other than the target compound in the reaction mixture will not inhibit reaction in the subsequent steps.

[0046] [Purifying process]

Purity of the target compound collected by the above methods can be increased by appropriately carrying out recrystallization, various chromatography methods, or distillation.

[0047] When the collected target compound is a solid, purity of the target compound can usually be improved by recrystallization. For recrystallization there may be used a simple solvent or a multiple solvent mixture that does not react with the target compound. Specifically, the target compound may first be dissolved at room temperature or with heating in the simple solvent or solvent mixture that does not react with the target compound. The obtained mixture may then be cooled with ice water or the like or allowed to stand at room temperature to cause precipitation of the target compound from the mixture.

[0048] When the collected target compound is a solid or liquid, purity of the target compound can be improved by various chromatography methods. In most cases a weakly acidic silica gel such as silica gel 60 (70-230 mesh or 340-400 mesh) by Merck, Ltd. or BW-300 (300 mesh) by Fuji Silysia Chemical, Ltd. may be used. If the target compound is basic, there may be used propylamine-coated silica gel (200-350 mesh) by Fuji Silysia Chemical, Ltd., or the like. If the target compound is dipolar or requires elution with a highly polar solvent such as methanol, there may be used NAM-200H or NAM-300H by Nagara Science Co., Ltd. Using these silica gels, the target compound may be eluted in a simple solvent or solvent mixture that does not react with the target compound and the solvent distilled off to obtain the target compound with enhanced purity.

[0049] When the collected target compound is a liquid, purity of the target compound can also be improved by distillation. The temperature and degree of reduced pressure may be adjusted as appropriate depending on the target compound, to obtain the target compound by an ordinary distillation method.

[0050] When a compound of the invention is obtained in free form, it may be converted to an acceptable salt of the compound by an ordinary method.

[0051] Conversely, when a compound of the invention is obtained as a salt, it may be converted to the free form of the compound by an ordinary method.

[0052] Various isomers (for example, geometric isomers, optical isomers, rotational isomers, stereoisomers, tautomers and the like) obtained for compounds of the invention may be purified and isolated using ordinary separation means such as, for example, recrystallization, a diastereomer salt method, enzymatic resolution or various chromatography methods (for example, thin-layer chromatography, column chromatography, gas chromatography, etc.).

[0053] [Formulation]

When a compound of the invention is to be used as a drug, the compound of the invention will usually be used after mixture and formulation with appropriate additives. However, this does not negate the use of the compounds of the invention in bulk forms as drugs.

[0054] As additives there may be mentioned excipients, binders, lubricants, disintegrators, coloring agents, taste correctives, emulsifiers, surfactants, dissolving aids, suspending agents, isotonizing agents, buffering agents, antiseptic agents, antioxidants, stabilizers, absorption accelerators and the like which are commonly used in drugs, and these may also be used in appropriate combinations as desired.

As examples of excipients there may be mentioned lactose, white soft sugar, glucose, corn starch, mannitol, sorbitol, starch, pregelatinized starch, dextrin, crystalline cellulose, light silicic anhydride, aluminum silicate, calcium silicate, magnesium aluminometasilicate, calcium hydrogenphosphate and the like.

As examples of binders there may be mentioned polyvinyl alcohol, methylcellulose, ethylcellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, polyvinylpyrrolidone, macrogol and the like.

As examples of lubricants there may be mentioned magnesium stearate, calcium stearate, sodium stearyl fumarate, talc, polyethylene glycol, colloidal silica and the like.

As examples of disintegrators there may be mentioned crystalline cellulose, agar, gelatin, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, pectin, low-substituted hydroxypropylcellulose, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethyl starch, carboxymethyl starch sodium and the like.

As coloring agents there may be mentioned those approved for addition to pharmaceuticals, such as iron sesquioxide, yellow iron sesquioxide, calamine, caramel, β-carotene, titanium oxide, talc, riboflavin sodium phosphate, yellow aluminum lake and the like.

As taste correctives there may be mentioned cocoa powder, menthol, aromatic powders, peppermint oil, camphor, cinnamon powder and the like.

As emulsifying agents or surfactants there may be mentioned stearyl

triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, glycerin monostearate, sucrose fatty acid esters, glycerin fatty acid esters and the like.

As dissolving aids there may be mentioned polyethylene glycol, propylene glycol, benzyl benzoate, ethanol, cholesterol, triethanolamine, sodium carbonate, sodium citrate, polysorbate 80, nicotinamide and the like.

As suspending agents there may be mentioned the aforementioned surfactants, as well as hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose.

As isotonizing agents there may be mentioned glucose, sodium chloride, mannitol, sorbitol and the like.

As buffering agents there may be mentioned phosphate, acetate, carbonate and citrate buffering solutions.

As antiseptic agents there may be mentioned methylparaben, propylparaben, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

As antioxidants there may be mentioned sulfite, ascorbic acid, α-tocopherol and the like.

As stabilizers there may be mentioned those commonly used in drugs.

As absorption accelerators there may also be mentioned those commonly used in drugs.

[0055] As formulations there may be mentioned oral forms such as tablets, powders, granules, capsules, syrups, lozenges and inhalants; external preparations such as suppositories, ointments, eye salves, tapes, eye drops, nose drops, ear drops, poultices, lotions, and the like; and injections.

The aforementioned oral forms may be formulated with appropriate combinations of the additives mentioned above. Their surfaces may also be coated if necessary.

The aforementioned external preparations may be formulated with appropriate combinations of the additives mentioned above, and especially excipients, binders, taste correctives, emulsifiers, surfactants, dissolving aids, suspending agents, isotonizing agents, antiseptic agents, antioxidants, stabilizers

and absorption accelerators.

Injections may also be formulated with appropriate combinations of the additives mentioned above, and especially emulsifiers, surfactants, dissolving aids, suspending agents, isotonizing agents, buffering agents, antiseptic agents, antioxidants, stabilizers and absorption accelerators.

[0056] The dosage of a drug according to the invention will differ depending on the severity of symptoms, patient age, gender and body weight, type of dosage form/salt, patient drug sensitivity and specific nature of the disease, but the dosage per day for adults will generally be 30 μg to 10 g (preferably 0.1 mg to 1 g) for oral administration, 30 μg to 20 g (preferably 100 μg to 10 g) for external application and 30 μg to 1 g (preferably 100 μg to 1 g) for injection, either administered at a single time or divided into several dosages.

These values are the actual administered amounts in the case of oral formulations and injections, and are the amounts actually absorbed by the body in the case of external formulations.

Examples

[0057] The compounds of the invention may be produced by the processes described in the following examples, and the effects of the compounds may be confirmed by the methods described in the following testing examples. However, these specific examples are merely illustrative and not intended to restrict the invention in any way, while various modifications may be implemented such as are within the scope of the invention.

[0058] Compounds mentioned with reference to published documents were produced in the manner described in those documents.

[0059] The symbols used throughout the present specification stand for the followings.

^{1}H-NMR: Proton nuclear magnetic resonance

δ: Chemical shift

s: singlet

d: doublet

t: triplet

q: quartet

m: multiplet

dd: double doublet

br.s: broad singlet

sept: septet

J: coupling constant

Hz: Hertz

M: mol/L

n-: normal

s-: secondary

tert-: tertiary (tertiary)

N: Normality

$CDCl_3$: deuterio-chloroform

DMSO-d_6: deuterio-dimethyl sulfoxide

DMF: *N,N*-Dimethylformamide

DME: 1,2-Dimethoxyethane

THF: Tetrahydrofuran

DMSO: Dimethyl sulfoxide

NMP: *N*-Methylpyrrolidinone

WSCD: Water-soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride [CAS No.25952-53-8]

4AMS: Molecular sieves 4A (pore size: 4 angstrom)

Me: Methyl

EGTA: Glycol ether diamine tetraacetic acid (O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid)

BSA: Bovine serum albumin

"Under reduced pressure" means conditions with approximately 1 to 50 mmHg by using a vacuum pump, a water-jet pump etc.

[0060] Unless otherwise specified, the "silica gel" in "silica gel column chromatography" mentioned throughout the examples is Silica Gel 60 (70-230 mesh or 340-400 mesh) by Merck, Ltd., FLASH+Cartridge (KP-SIL, pore size: 60 angstrom, particle size: 32-63 μm) by Biotage, or Cartridge (Hi-Flash, pore size: 60 angstrom, particle size: 40 μm) by Yamazen.

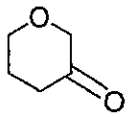
[0061] Also unless otherwise specified, the "(NH)silica gel" in "(NH)silica gel column chromatography" mentioned throughout the examples is propylamine-

coated silica gel (200-350 mesh) by Fuji Silysia Chemical, Ltd., or Cartridge (Hi-Flash Amino, pore size: 60 angstrom, particle size: 40 μm) by Yamazen.

[0062] The term "room temperature" refers to a range from about 10°C to 35°C. The percentage values are weight percentages, unless otherwise specified.

[0063] [Production Example 1A] Dihydro-2*H*-pyran-3(4H)-one

[Chemical Formula 8]



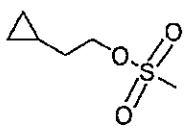
To a mixture of oxalyl chloride (2.28 mL, 26.6 mmol) and dichloromethane (40 mL) was added a mixture of DMSO (3.78 mL, 53.2 mmol) and dichloromethane (20 mL) while stirring at -78°C, and the mixture was stirred at -78°C for 30 minutes. After then adding to this mixture a mixture of tetrahydropyran-3-ol (synthesized according to the method described in Tetrahedron, 60, 10411-10418, 2004) (1.36 g, 13.3 mmol) and dichloromethane (20 mL) at -78°C, the resulting mixture was stirred at -78°C for 30 minutes, after which triethylamine (11.1 mL, 79.8 mmol) was added and stirring was continued for 2 hours while slowly raising the temperature to 0°C.

Brine and diethyl ether were added to the mixture, and after sufficient shaking, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was then filtered, and the solvent in the filtrate was distilled off under reduced pressure to obtain the title compound (1.62 g, 16.2 mmol).

^{1}H-NMR ($CDCl_3$) δ: 2.07-2.14 (m, 2H), 2.54 (t, J = 6.8 Hz, 2H), 3.82-3.88 (m, 2H), 4.03 (s, 2H).

[0064] [Production Example 1B] 2-Cyclopropylethyl methanesulfonate

[Chemical Formula 9]



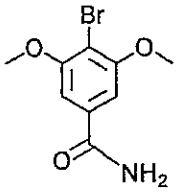
To a mixture of 2-cyclopropylethanol (5.35 g, 62.1 mmol) and dichloromethane (107 mL) were added methanesulfonyl chloride (5.29 mL, 68.3 mmol) and triethylamine (13.1 mL, 93.1 mmol) in that order while stirring on ice,

and the resulting mixture was stirred for 1 hour. Water and ethyl acetate were then added to the reaction mixture. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was then filtered, and the solvent in the filtrate was distilled off under reduced pressure to obtain the title compound (10.3 g, 62.7 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.10-0.16 (m, 2H), 0.48-0.55 (m, 2H), 0.72-0.83 (m, 1H), 1.65 (q, J = 6.8 Hz, 2H), 3.01 (s, 3H), 4.29 (t, J = 6.8 Hz, 2H).

[0065] [Production Example 1C (1)] 4-Bromo-3,5-dimethoxybenzamide

[Chemical Formula 10]

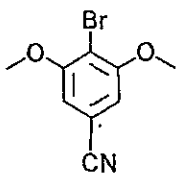


To a mixture of 4-bromo-3,5-dimethoxybenzoic acid (15 g, 57.6 mmol) and THF (200 mL) were added triethylamine (9.63 mL, 69.0 mmol) and ethyl chloroformate (5.79 mL, 60.6 mmol) while stirring on ice, and the resulting mixture was stirred for 20 minutes while cooling on ice. After adding 28% aqueous ammonia to the mixture and stirring at room temperature for 2 hours, ethyl acetate was further added. After then thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and the solvent in the filtrate was distilled off under reduced pressure. The obtained residue (solid) was washed with diethyl ether and collected by filtration to obtain the title compound (11.8 g, 45.4 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.95 (s, 6H), 7.00 (s, 2H).

[0066] [Production Example 1C (2)] 4-Bromo-3,5-dimethoxybenzonitrile

[Chemical Formula 11]



After adding toluene (20 mL), DMF (5 mL) and thionyl chloride (3.36 mL,

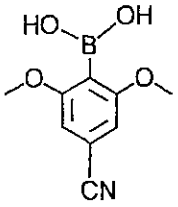
46.1 mmol) to 4-bromo-3,5-dimethoxybenzamide (4 g, 15.4 mmol) in that order, the mixture was stirred at 50°C for 1 hour. Ice water was added to the mixture at room temperature, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

The obtained residue (solid) was washed with diethyl ether/*n*-heptane (1/1) to obtain the title compound (2.08 g, 8.59 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.93 (s, 6H), 6.82 (s, 2H).

[0067] [Production Example 1C (3)] (4-Cyano-2,6-dimethoxyphenyl)boronic acid

[Chemical Formula 12]



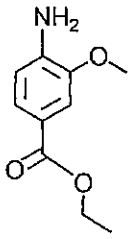
To a mixture of 4-bromo-3,5-dimethoxybenzonitrile (2 g, 8.26 mmol) and THF (60 mL) was added *n*-butyllithium (1.58 M solution in *n*-hexane: 5.48 mL, 8.68 mmol) while stirring at -100°C, and stirring was continued at -100°C for 30 minutes. After then adding trimethyl borate (1.84 mL, 16.5 mmol), stirring was continued for 4 hours while raising the temperature to -20°C. A saturated aqueous solution of ammonium chloride and 1N hydrochloric acid were then added to the reaction mixture, and ethyl acetate was added.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The obtained residue (solid) was washed with *n*-heptane to obtain the title compound (1.43 g, 6.91 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.96 (s, 6H), 6.89 (s, 2H), 7.01 (s, 2H).

[0068] [Production Example 2C (1)] Ethyl 4-amino-3-methoxybenzoate

[Chemical Formula 13]



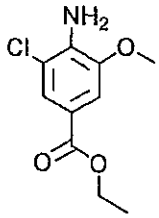
To a mixture of 4-amino-3-methoxybenzoic acid (15 g, 89.7 mmol) and ethanol (170 mL) was added concentrated sulfuric acid (5 mL), and the mixture was heated to reflux for 7 hours. The reaction mixture was then returned to room temperature. The solvent in the filtrate was distilled off under reduced pressure. Water, a saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate were added to the residue

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was then filtered, and the solvent in the filtrate was distilled off under reduced pressure to obtain the title compound (17.8 g, 91.2 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.37 (t, J = 6.8 Hz, 3H), 3.90 (s, 3H), 4.32 (q, J = 6.8 Hz, 2H), 6.66 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 1.6 Hz, 1H), 7.54 (dd, J = 1.6, 8.0 Hz, 1H).

[0069] [Production Example 2C (2)] Ethyl 4-amino-3-chloro-5-methoxybenzoate

[Chemical Formula 14]

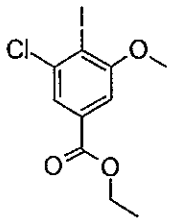


After adding acetonitrile (170 mL) and *N*-chlorosuccinimide (13.4 g, 100 mmol) to ethyl 4-amino-3-methoxybenzoate (17.8 g, 91.2 mmol) in that order, the mixture was stirred at 60°C for 2 hours. The mixture was returned to room temperature, and the solvent in the mixture was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 8/1 then 4/1) to obtain the title compound (15.8 g, 68.8 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.37 (t, J = 6.8 Hz, 3H), 3.91 (s, 3H), 4.32 (q, J = 6.8 Hz, 2H), 4.58 (br.s, 2H), 7.36 (d, J = 1.8 Hz, 1H), 7.65 (d, J = 1.8 Hz, 1H).

[0070] [Production Example 2C (3)] Ethyl 3-chloro-4-iodo-5-methoxybenzoate

[Chemical Formula 15]

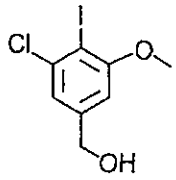


To ethyl 4-amino-3-chloro-5-methoxybenzoate (15.8 g, 68.8 mmol) were added acetonitrile (40 mL) and diiodomethane (22.2 mL, 275 mmol) in that order, and then the mixture was stirred at 70°C and isoamyl nitrite (13.9 mL, 103 mmol) was added dropwise over a period of 10 minutes. The mixture was then stirred at 70°C for 40 minutes. After returning the mixture to room temperature, the solvent in the mixture was distilled off under reduced pressure and the residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 8/1 then 5/1) to obtain the title compound (15.6 g, 45.8 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.40 (t, J = 7.2 Hz, 3H), 3.95 (s, 3H), 4.38 (q, J = 7.2 Hz, 2H), 7.30 (d, J = 1.6 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H).

[0071] [Production Example 2C (4)] (3-Chloro-4-iodo-5-methoxyphenyl)methanol

[Chemical Formula 16]



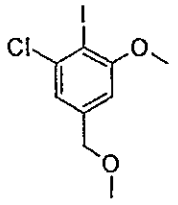
To a mixture of ethyl 3-chloro-4-iodo-5-methoxybenzoate (15.6 g, 45.8 mmol) and toluene (150 mL) was added diisobutylaluminum hydride (1.01 M solution in toluene: 95.2 mL, 96.2 mmol) while stirring at -78°C, and stirring was continued for 3 hours while raising the temperature to -30°C. After then adding a solution of Rochelle salt (sodium potassium (+)-tartrate tetrahydrate) (77.6 g, 275 mmol) in water (400 mL) to the mixture, stirring was continued for 5 hours at room temperature and ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was then filtered, and the

solvent in the filtrate was distilled off under reduced pressure to obtain the title compound (13.7 g, 45.8 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.90 (s, 3H), 4.66 (s, 2H), 6.72 (d, J = 1.2 Hz, 1H), 7.09 (br., 1H).

[0072] [Production Example 2C (5)] 1-Chloro-2-iodo-3-methoxy-5-(methoxymethyl)benzene

[Chemical Formula 17]



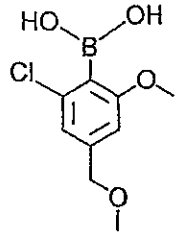
To a mixture of (3-chloro-4-iodo-5-methoxyphenyl)methanol (13.7 g, 45.9 mmol) and NMP (90 mL) were added sodium hydride (60% dispersion in oil: 2.02 g, 50.5 mmol) and iodomethane (3.14 mL, 50.4 mmol), and the mixture was stirred at room temperature for 4 hours. Water and diethyl ether were added to the mixture. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 8/1 then 4/1) to obtain the title compound (13.2 g, 42.2 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.40 (s, 3H), 3.90 (s, 3H), 4.40 (s, 2H), 6.69 (s, 1H), 7.07 (s, 1H).

[0073] [Production Example 2C (6)] [2-Chloro-6-methoxy-4-(methoxymethyl)phenyl]boronic acid

[Chemical Formula 18]



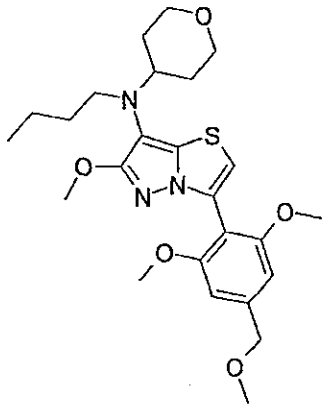
To a mixture of 1-chloro-2-iodo-3-methoxy-5-(methoxymethyl)benzene (4.72 g, 15.1 mmol) and THF (150 mL) was added *n*-butyllithium (1.58 M solution in *n*-hexane: 10.5 mL, 16.6 mmol) while stirring at -100°C, and stirring was continued for 30 minutes at -100°C to -85°C. After then adding trimethyl borate (4.21 mL, 37.8 mmol), stirring was continued for 4 hours while slowly raising the temperature to -20°C. A saturated aqueous solution of ammonium chloride and 1N hydrochloric acid were then added to the reaction mixture, and ethyl acetate was further added.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The obtained residue (solid) was washed with *n*-heptane to obtain the title compound (2.65 g, 11.5 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.42 (s, 3H), 3.92 (s, 3H), 4.44 (s, 2H), 6.23 (s, 2H), 6.86 (s, 1H), 7.00 (br.s, 1H).

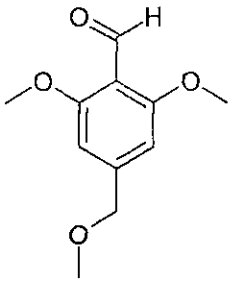
[0074] Example 1 *N*-Butyl-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 19]



[0075] (1a) 2,6-Dimethoxy-4-(methoxymethyl)benzaldehyde

[Chemical Formula 20]



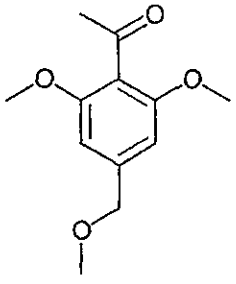
To a mixture of 1,3-dimethoxy-5-methoxymethyl-2-bromobenzene (Production Example 8X of WO 04/037822) (33.8 g, 129 mmol) and tetrahydrofuran (338 mL) was added *n*-butyllithium (2.77 M solution in *n*-hexane: 55.9 mL, 155 mmol) at -78°C. After stirring the mixture at -78°C for 30 minutes, DMF (11 mL, 142 mmol) was added and stirring was continued for 2 hours while heating to room temperature. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction mixture.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/1 then 1/1) to obtain the title compound (16.3 g, 77.5 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.45 (s, 3H), 3.91 (s, 6H), 4.46 (s, 2H), 6.56 (s, 2H), 10.48 (s, 1H).

[0076] (1b) 1-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]ethanone

[Chemical Formula 21]



To a mixture of 2,6-dimethoxy-4-(methoxymethyl)benzaldehyde (16.3 g, 77.5 mmol) and THF (200 mL) was added methylmagnesium bromide (0.99 M solution in *n*-hexane: 95.9 mL, 93 mmol) at 0°C, and the mixture was stirred for 30 minutes. A saturated aqueous solution of ammonium chloride and ethyl acetate

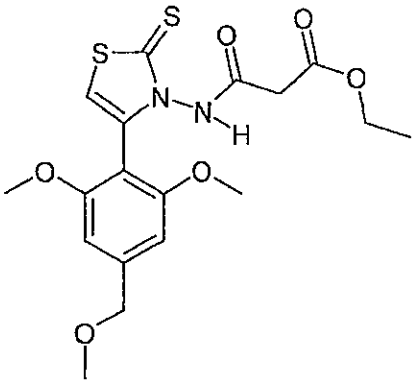
were added to the reaction mixture at 0°C.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. Dichloromethane-acetonitrile (9:1,160 mL), 4ÅMS (38 g), 4-methylmorpholine-4-oxide (14.6 g, 121 mmol) and tetrapropylammonium perruthenate (1.41 g, 4.02 mmol) were added to the obtained residue in that order and the mixture was stirred at room temperature for 13 hours. Ethyl acetate was added to the mixture, and silica gel column chromatography was performed for suction filtration. The solvent in the obtained filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/1 then 1/2) to obtain the title compound (16.8 g, 75.1 mmol).

^{1}H-NMR ($CDCl_3$) δ: 2.47 (s, 3H), 3.41 (s, 3H), 3.81 (s, 6H), 4.44 (s, 2H), 6.54 (s, 2H).

[0077] (1c) Ethyl 3-{[4-(2,6-dimethoxy-4-(methoxymethyl)phenyl]-2-thioxo-1,3-thiazole-3(2H)-yl]-amino}-3-oxopropanoate

[Chemical Formula 22]



After adding tetrahydrofuran (140 mL) and triethylamine (56.1 mL, 403 mmol) to 1-[2,6-dimethoxy-4-(methoxymethyl)phenyl]ethanone (22.7 g, 102 mmol), *tert*-butyldimethylsilyl trifluoromethanesulfonic acid (33.1 mL, 145 mmol) was slowly added dropwise at 0°C and the mixture was stirred for 30 minutes. To this mixture was added *N*-bromosuccinimide (18.8 g, 107 mmol) at 0°C, and stirring was continued for 1.5 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the mixture, and ethyl acetate was added.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Tetrabutylammonium fluoride (1.0 M solution in THF: 91.4 mL, 91.4 mmol) was added to a mixture of the obtained residue and tetrahydrofuran (140 mL) at 0°C, and the mixture was stirred for 30 minutes. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction mixture at 0°C.

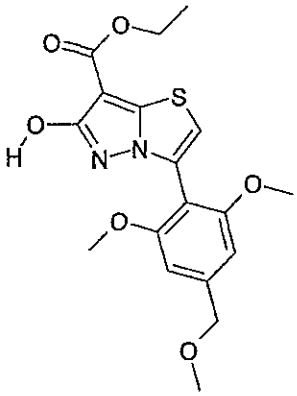
After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 3/1 then 2/1).

To a mixture of the obtained residue and water-ethanol (2:1, 275 mL) was added potassium hydrazinecarbodithioate (Heterocycles, vol.23, No.12, 1985, 3099-3106) at 4°C, and the mixture was stirred for 20 hours. The mixture was suction filtered with a glass filter, and the residue was washed with water and dried under reduced pressure. To a mixture of the obtained residue and dichloromethane (400 mL) was added dropwise ethylmalonyl chloride (8.86 mL, 66.6 mmol) at 0°C, and the mixture was stirred at room temperature for 30 minutes. The solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/1 then 1/3) to obtain the title compound (11.7 g, 27.6 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.24 (t, J = 7.2 Hz, 3H), 3.33 (br.s, 2H), 3.44 (s, 3H), 3.82 (s, 6H), 4.14 (q, J = 7.2 Hz, 2H), 4.45 (s, 2H), 4.49 (s, 1H), 6.57 (s, 2H), 9.67 (s, 1H).

[0078] (1d) Ethyl 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-hydroxypyrazolo[5,1-*b*][1,3]thiazole-7-carboxylate

[Chemical Formula 23]

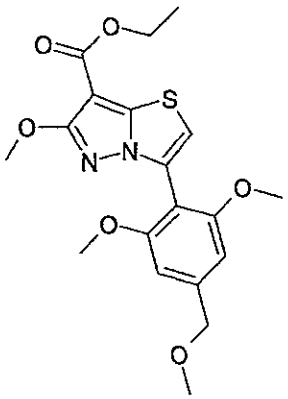


Acetone (235 mL) was added to ethyl 3-{[4-(2,6-dimethoxy-4-(methoxymethyl)phenyl]-2-thioxo-1,3-thiazole-3(2*H*)-yl]-amino}-3-oxopropanoate (11.7 g, 27.6 mmol), and then iodomethane (17.1 mL, 276 mmol) was added dropwise at room temperature and the mixture was stirred for 23 hours. The solvent in the filtrate was distilled off under reduced pressure. To the obtained residue were added *tert*-butanol (235 mL) and potassium *tert*-butoxide in that order, and the mixture was stirred at room temperature for 3.5 hours. Water was added to the mixture while cooling on ice, and then aqueous 2N hydrochloric acid was added until the pH of the mixture reached approximately 4. The precipitated solid was collected by filtration, and the resulting residue was washed with water and dried under reduced pressure to obtain the title compound (6.3 g, 16 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.41 (t, J = 6.8 Hz, 3H), 3.44 (s, 3H), 3.75 (s, 6H), 4.39 (q, J = 6.8 Hz, 2H), 4.49 (s, 2H), 6.62 (s, 2H), 6.72 (s, 1H).

[0079] (1e) Ethyl 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazole-7-carboxylate

[Chemical Formula 24]



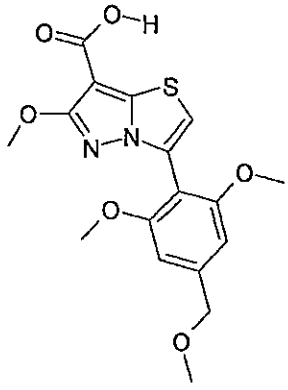
After adding DMF (164 mL), cesium carbonate (26 g, 80.1 mmol) and iodomethane (4.99 mL, 80.1 mmol) in that order to ethyl 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-hydroxypyrazolo[5,1-*b*][1,3]thiazole-7-carboxylate (6.3 g, 16 mmol), the mixture was stirred at 70°C for 15 hours.

Water and ethyl acetate were then added to the reaction mixture while cooling on ice. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/2) to obtain the title compound (2.8 g, 6.89 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.38 (t, J = 7.2 Hz, 3H), 3.47 (s, 3H), 3.77 (s, 6H), 3.96 (s, 3H), 4.33 (q, J = 7.2 Hz, 2H), 4.51 (s, 2H), 6.65 (s, 2H), 6.71 (s, 1H).

[0080] (1f) 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazole-7-carboxylic acid

[Chemical Formula 25]

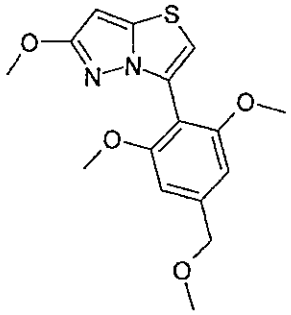


After adding ethanol (124 mL) and aqueous 5N sodium hydroxide (11 mL, 55 mmol) in that order to ethyl 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazole-7-carboxylate (2.8 g, 6.89 mmol), the mixture was heated to reflux for 2 hours. Aqueous 5N hydrochloric acid (11 mL) was then added to the mixture while cooling on ice, and the solvent in the mixture was distilled off under reduced pressure. Water was added to the residue, and the precipitated solid was collected by filtration, washed with water and dried under reduced pressure to obtain the title compound (2.52 g, 6.66 mmol).

^{1}H-NMR (DMSO-d_6) δ: 3.38 (s, 3H), 3.72 (s, 6H), 3.79 (s, 3H), 4.48 (s, 2H), 6.76 (s, 2H), 7.16 (s, 1H).

[0081] (1g) 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazole

[Chemical Formula 26]



After adding an aqueous solution of polyphosphoric acid (2.6 wt%: 214 mL) to 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazole-7-carboxylic acid (2.52 g, 6.66 mmol), the mixture was heated at 120°C for 3.5 hours. Water and ethyl acetate were then added to the reaction mixture at room temperature.

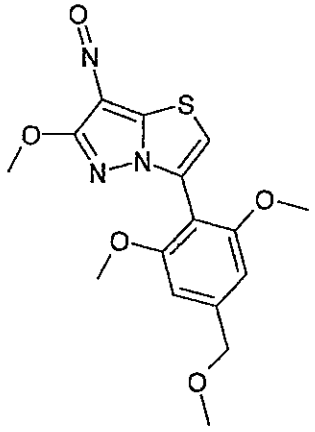
After thoroughly shaking the mixture, the organic layer was separated and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by (NH)silica gel column chromatography (ethyl acetate) to obtain the title compound (2.17 g, 6.47 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.46 (s, 3H), 3.77 (s, 6H), 3.89 (s, 3H), 4.50 (s, 2H), 5.84 (s, 1H), 6.40 (s, 1H), 6.63 (s, 2H).

[0082] (1h) 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-7-

nitrosopyrazolo[5,1-*b*][1,3]thiazole

[Chemical Formula 27]

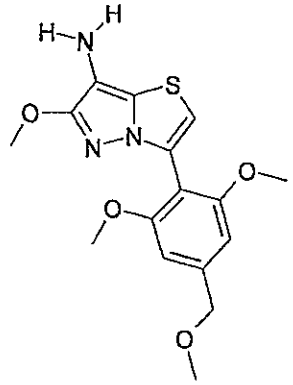


A mixture of water and 5N hydrochloric acid (1:4, 70 mL) was added to 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazole (2.17 g, 6.47 mmol), and then sodium nitrite (1.06 g, 15.3 mmol) was added at 0°C and the mixture was stirred for 1 hour. Aqueous 5N sodium hydroxide and ethyl acetate were added to the mixture at room temperature. After thoroughly shaking the mixture, the organic layer was separated and dried over anhydrous magnesium sulfate. The mixture was then filtered, and the solvent in the filtrate was distilled off under reduced pressure to obtain the title compound (2.34 g, 6.44 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.49 (s, 3H), 3.79 (s, 6H), 4.23 (s, 3H), 4.52 (s, 2H), 6.66 (s, 2H), 6.90 (s, 1H).

[0083] (1i) 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 28]



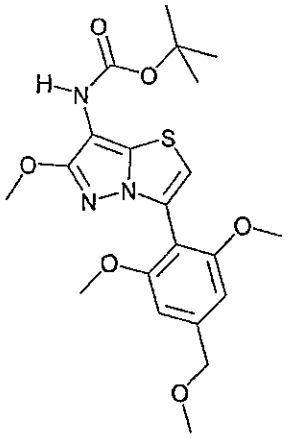
Ethyl acetate (109 mL) and 10% palladium-carbon powder (50% wet: 2.34

g, 2.2 mmol) were added in that order to 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-7-nitrosopyrazolo[5,1-*b*][1,3]thiazole (2.34 g, 6.44 mmol), and the mixture was stirred for 1 hour under a hydrogen atmosphere. The mixture was filtered with Celite and the solvent in the obtained filtrate was distilled off under reduced pressure. The residue was purified by (NH)silica gel column chromatography (ethyl acetate) to obtain the title compound (1.43 g, 4.09 mmol).

^{1}H-NMR ($CDCl_3$) δ: 2.60 (br.s, 2H), 3.46 (s, 3H), 3.77 (s, 6H), 3.89 (s, 3H), 4.50 (s, 2H), 6.40 (s, 1H), 6.64 (s, 2H).

[0084] (1j) *tert*-Butyl {3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate

[Chemical Formula 29]

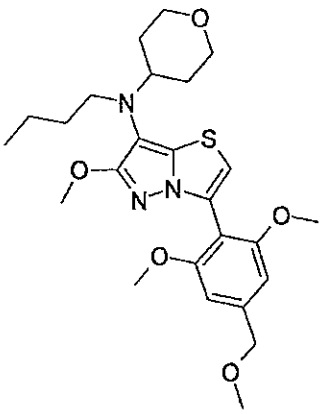


Dichloromethane (50 mL), triethylamine (0.3 mL, 2.15 mmol) and di-*tert*-butyl dicarbonate (375 mg and 1.72 mmol) were added in that order to 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazole-7-amine (500 mg, 1.43 mmol), and the mixture was stirred at room temperature for 22 hours. The solvent in the mixture was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/1 then 1/2) to obtain the title compound (511 mg, 1.14 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 9H), 3.46 (s, 3H), 3.75 (s, 6H), 3.88 (s, 3H), 4.49 (s, 2H), 6.08 (br.s, 1H), 6.43 (s, 1H), 6.63 (s, 2H).

[0085] (1k) *N*-Butyl-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 30]



Sodium hydride (60% dispersion in oil: 8.1 mg, 0.203 mmol) was added to a mixture of *tert*-butyl {3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (70 mg, 0.156 mmol) and DMF (6 mL) at room temperature, and the mixture was stirred for 30 minutes. To this mixture was added dropwise 1-iodobutane (0.024 mL, 0.203 mmol) at room temperature, and stirring was continued for 1 hour. Water and ethyl acetate were then added to the reaction mixture while cooling on ice.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Dichloromethane (5 mL) and trifluoroacetic acid (1 mL) were added in that order to the residue, and the mixture was stirred at room temperature for 1 hour. The solvent in the filtrate was distilled off under reduced pressure. After then adding methanol (6 mL), tetrahydro-4*H*-pyran-4-one (0.03 mL, 0.312 mmol) and acetic acid (1 mL) in that order to the residue at room temperature, α-picolineborane (33.4 mg, 0.312 mmol) was added at 0°C and the mixture was stirred for 1 hour. To this mixture was added a 5N aqueous solution of sodium hydroxide to approximate neutral pH of the mixture while cooling on ice, and then ethyl acetate was added.

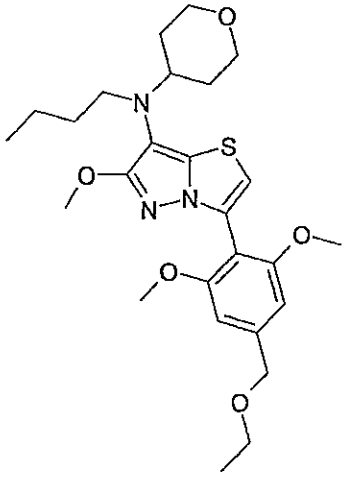
After thoroughly shaking the mixture, the organic layer was separated and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was

purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/3) to obtain the title compound (61 mg, 0.125 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.86(t, J = 7.2 Hz, 3H), 1.22-1.42 (m, 4H), 1.56-1.68 (m, 2H), 1.77-1.88 (m, 2H), 2.97 (t, J = 7.2 Hz, 2H), 3.00-3.11 (m, 1H), 3.33 (td, J = 1.6, 11.6 Hz, 2H), 3.47 (s, 3H), 3.79 (s, 6H), 3.86 (s, 3H), 3.92-4.03 (m, 2H), 4.50(s, 2H), 6.42 (s, 1H), 6.65(s, 2H).

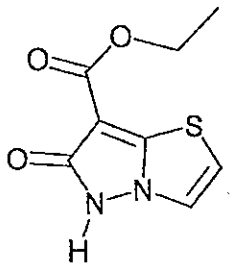
[0086] Example 2 *N*-Butyl-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 31]



[0087] (2a) Ethyl 6-oxo-5,6-dihydropyrazolo[5,1-*b*][1,3]thiazole-7-carboxylate

[Chemical Formula 32]



To a mixture of diethyl malonate (100 g, 624 mmol) and DMF (900 mL) were added cesium carbonate (488 g, 1.5 mol) and carbon disulfide (45.3 mL, 749 mmol) while stirring at room temperature, and then stirring was continued at room temperature for 5 minutes. After adding bromoacetaldehydediethylacetal (290 mL, 1.87 mol) dropwise to the mixture at room temperature, sodium iodide (9.34 g,

62.4 mmol) was added and the mixture was stirred at 60°C for 8 hours. Water and diethyl ether were added to the mixture at room temperature.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

To a mixture of the obtained residue and ethanol (900 mL) was added hydrazine hydrate (60.7 mL, 1.25 mol) while stirring in a water bath, and the mixture was stirred at room temperature for 13 hours. The mixture was filtered and the solvent in the filtrate was distilled off under reduced pressure.

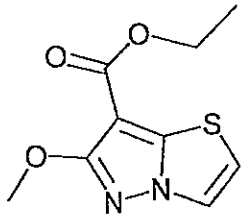
To the obtained residue were added 1,4-dioxane (1L) and 5N hydrochloric acid (200 mL) in that order, and the mixture was stirred at 60°C for 4 hours. The mixture was returned to room temperature, and the solvent in the mixture was distilled off under reduced pressure. Water was added to the resulting residue, and the mixture was filtered to obtain a filtered residue and filtrate. The residue was washed with water and then dried under reduced pressure to obtain the title compound (42.5 g, 200 mmol).

Ethyl acetate was added to the obtained filtrate. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. Diethyl ether was added to the resulting residue, and the precipitated solid was filtered and dried under reduced pressure to obtain the title compound (2.6 g, 12.3 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.41 (t, J = 7.0 Hz, 3H), 4.40 (q, J = 7.0 Hz, 2H), 6.89 (d, J = 4.0 Hz, 1H), 7.69 (d, J = 4.4 Hz, 1H).

[0088] (2b) Ethyl 6-methoxypyrazolo[5,1-*b*][1,3]thiazole-7-carboxylate

[Chemical Formula 33]



To a mixture of ethyl 6-oxo-5,6-dihydropyrazolo[5,1-*b*][1,3]thiazole-7-

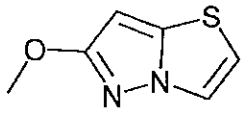
carboxylate (41.3 g, 195 mmol) and DMF (624 mL) were added cesium carbonate (127 g, 389 mmol) and iodomethane (24.2 mL, 389 mmol) while stirring at room temperature. The mixture was stirred at room temperature for 1 hour, and then water and a mixed solvent of ethyl acetate/diethyl ether (1/1) were added.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 9/1 then 1/2.3) to obtain the title compound (30.7 g, 136 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.39 (t, J = 7.0 Hz, 3H), 4.08 (s, 3H), 4.35 (q, J = 7.0 Hz, 2H), 6.87 (d, J = 4.4 Hz, 1H), 7.66 (d, J = 4.4 Hz, 1H).

[0089] (2c) 6-Methoxypyrazolo[5,1-*b*][1,3]thiazole

[Chemical Formula 34]



To a mixture of ethyl 6-methoxypyrazolo[5,1-*b*][1,3]thiazole-7-carboxylate (30.7 g, 136 mmol) and ethanol (407 mL) was added aqueous 5N sodium hydroxide (136 mL) while stirring at room temperature, and the mixture was stirred at 80°C for 2 hours. A suitable amount of 5N hydrochloric acid was then added while stirring on ice to approximate neutral pH of the mixture. Ethanol in the mixture was distilled off under reduced pressure. The precipitated solid in the mixture was collected by filtration and washed with water.

To the obtained residue were added 1,4-dioxane (400 mL) and concentrated hydrochloric acid (200 mL) in that order, and the mixture was stirred at 60°C for 1.5 hours. 1,4-Dioxane in the mixture was distilled off under reduced pressure. A suitable amount of sodium hydroxide was added to a weakly acidic pH of the mixture while stirring on ice, and then ethyl acetate was added.

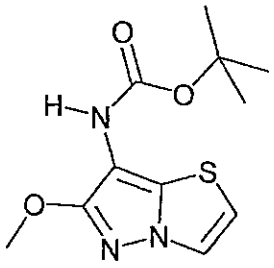
After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column

chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/0 then 2.3/1) to obtain the title compound (15.8 g, 103 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.95 (s, 3H), 5.81 (d, J = 0.8 Hz, 1H), 6.60 (d, J = 4.0 Hz, 1H), 7.58 (dd, J = 0.8, 4.4 Hz, 1H).

[0090] (2d) *tert*-Butyl (6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate

[Chemical Formula 35]



To a mixture of 6-methoxypyrazolo[5,1-*b*][1,3]thiazole (15.8 g, 103 mmol) and 5N hydrochloric acid (350 mL) was added a mixture of sodium nitrite (10.6 g, 154 mmol) and water (115 mL) while stirring on ice. After stirring the mixture at room temperature for 0.5 hour, aqueous 5N sodium hydroxide was added in an appropriate amount for approximate neutral pH of the mixture, while stirring on ice. The precipitate in the mixture was collected by filtration and washed with water.

Ethanol (200 mL), THF (300 mL) and 10% palladium-carbon (50% wet: 16 g) were added in that order to the obtained residue, and the mixture was stirred at room temperature for 5 hours at an atmospheric pressure under a hydrogen atmosphere. The mixture was filtered with Celite and the solvent in the obtained filtrate was distilled off under reduced pressure.

To a mixture of the obtained residue and dichloromethane (425 mL) were added di-*tert*-butyl dicarbonate (24.1 g, 111 mmol) and triethylamine (17.8 mL, 128 mmol) while stirring at room temperature, and the mixture was stirred at room temperature for 11 hours. The solvent in the mixture was distilled off under reduced pressure, and then the residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/1) to obtain the title compound (16.5 g, 61.4 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.51 (s, 9H), 3.98 (s, 3H), 6.12 (br.s, 1H), 6.54 (d, J = 4.0 Hz, 1H), 7.48 (d, J = 4.4 Hz, 1H).

[0091] (2d-2) Alternative synthesis method of *tert*-butyl (6-methoxypyrazolo[5,1-

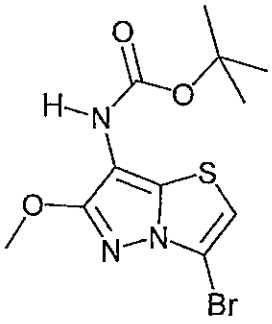
b][1,3]thiazol-7-yl)carbamate

To a mixture of 6-methoxypyrazolo[5,1-*b*]thiazole-7-carboxylic acid (300 mg, 1.51 mmol) and 1,4-dioxane (4 mL) were added triethylamine (0.215 mL, 1.54 mmol) and diphenylphosphoryl azide (0.325 mL, 1.51 mmol) while stirring at room temperature, and the mixture was stirred and heated to reflux for 3 hour. After returning the mixture to room temperature, triethylamine (0.631 mL, 4.53 mmol) and *tert*-butanol (0.289 mL, 3.02 mmol) were added and the mixture was stirred and heated to reflux for 3 hour. After returning the mixture to room temperature, the solvent in the mixture was distilled off under reduced pressure and the residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/4) to obtain the title compound (144 mg, 0.535 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.51 (s, 9H), 3.98 (s, 3H), 6.12 (br.s, 1H), 6.54 (d, J = 4.0 Hz, 1H), 7.48 (d, J = 4.4 Hz, 1H).

[0092] (2e) *tert*-Butyl (3-bromo-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate

[Chemical Formula 36]



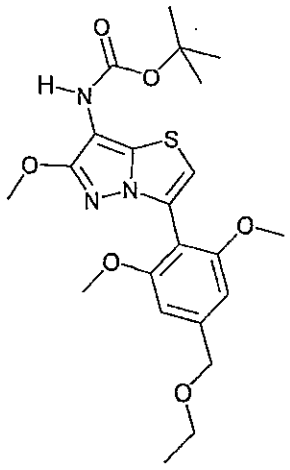
To a mixture of *tert*-butyl (6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate (16.5 g, 61.4 mmol) and THF (410 mL) was added *n*-butyllithium (2.77 M solution in *n*-hexane: 62.1 mL, 172 mmol) while stirring at -78°C. After further stirring the mixture at -78°C for 40 minutes, 1,2-dibromotetrafluoroethane (10.2 mL, 86 mmol) was added and stirring was continued for 2 hours while heating to room temperature. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the mixture, and then acetic acid was added to a weakly acidic pH of the mixture. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried

over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/0 then 4/1) to obtain the title compound (14.3 g, 41.1 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.51 (s, 9H), 4.04 (s, 3H), 6.16 (br.s, 1H), 6.50 (s, 1H).

[0093] (2f) *tert*-Butyl {3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate

[Chemical Formula 37]



To a mixture of *tert*-butyl (3-bromo-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate (2.00 g, 5.74 mmol), DME (200 mL) and water (70 mL) were added 2,6-dimethoxy-4-(ethoxymethyl)phenylboric acid (Production Example 33 of WO 04/037822) (2.07 g, 8.64 mmol), potassium carbonate (1.59 g, 11.5 mmol), triphenylphosphine (0.75 g, 2.87 mmol) and palladium acetate (0.13 g, 0.57 mmol) in that order, and the mixture was stirred at 90°C (internal temperature) for 4 hours. Water was added to the reaction mixture, and then ethyl acetate was added.

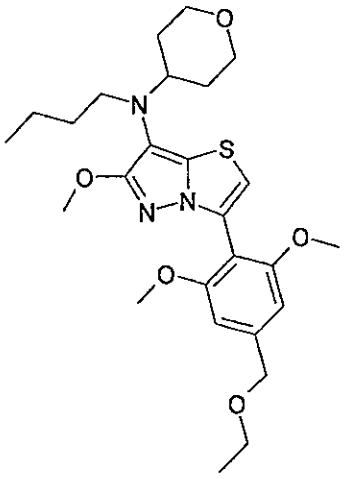
After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/1 then 1/1) to obtain the title compound (2.49 g, 5.37 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, J = 7.2 Hz, 3H), 1.52 (s, 9H), 3.61 (q, J = 7.2 Hz, 2H),

3.75 (s, 6H), 3.87 (s, 3H), 4.53 (s, 2H), 6.09 (br.s, 1H), 6.42 (s, 1H), 6.64 (s, 2H).

[0094] (2g) *N*-Butyl-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 38]



To a mixture of *tert*-butyl {3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (100 mg, 0.22 mmol) and DMF (5 mL) was added sodium hydride (60% dispersion in oil: 11.2 mg, 0.28 mmol) at room temperature, and the mixture was stirred for 30 minutes. After then adding 1-iodobutane (33.0 μL, 0.28 mmol) to the mixture, stirring was continued for 30 minutes. Water was added to the mixture while cooling on ice, and then ethyl acetate was added.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Dichloromethane (5 mL) was added to the resulting residue, trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the filtrate was distilled off under reduced pressure.

THF (10 mL) was then added to the resulting residue, tetrahydro-4*H*-pyran-4-one (42.2 μL, 0.43 mmol), acetic acid (1 mL) and sodium triacetoxyborohydride (91.6 mg, 0.43 mmol) were added in that order, and the mixture was stirred at room temperature for 14 hours.

To this mixture was added aqueous 5N sodium hydroxide to approximate

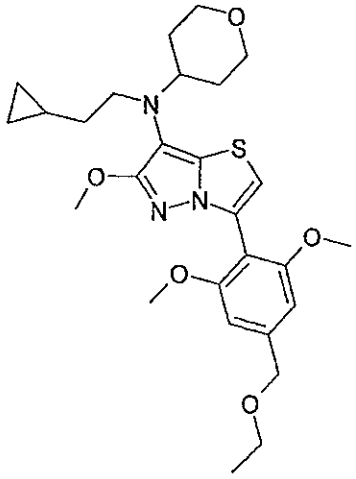
neutral pH of the mixture while cooling on ice, and then ethyl acetate was added.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/1 then 1/1) to obtain the title compound (81.0 mg, 0.16 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, J = 6.8 Hz, 3H), 1.30 (t, J = 6.8 Hz, 3H), 1.24-1.40 (m, 4H), 1.52-1.67 (m, 2H), 1.78-1.87 (m, 2H), 2.97 (t, J = 6.8 Hz, 2H), 2.99-3.11 (m, 1H), 3.38 (td, J = 1.6, 11.6 Hz, 2H), 3.63 (q, J = 7.2 Hz, 2H), 3.79 (s, 6H), 3.86 (s, 3H), 3.94-4.03 (m, 2H), 4.55 (s, 2H), 6.41 (s, 1H), 6.66 (s, 2H).

[0095] Example 3 *N*-(2-Cyclopropylethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 39]



To a mixture of *tert*-butyl {3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (100 mg, 0.216 mmol) and DMSO (5 mL) were added powdered sodium hydroxide (17.3 mg, 0.432 mmol) and 2-cyclopropylethyl methanesulfonate (70.9 mg, 0.432 mmol) in that order at room temperature, and the mixture was stirred for 1 hour. Water was added to the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was

filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Dichloromethane (5 mL) was added to the resulting residue, trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the filtrate was distilled off under reduced pressure.

THF (10 mL) was then added to the resulting residue, tetrahydro-4*H*-pyran-4-one (42.2 μL, 0.432 mmol), acetic acid (1 mL) and sodium triacetoxyborohydride (91.6 mg, 0.432 mmol) were added in that order, and the mixture was stirred at room temperature for 4 hours.

To this mixture there was added aqueous 5N sodium hydroxide to approximate neutral pH of the mixture while cooling on ice, and then ethyl acetate was added.

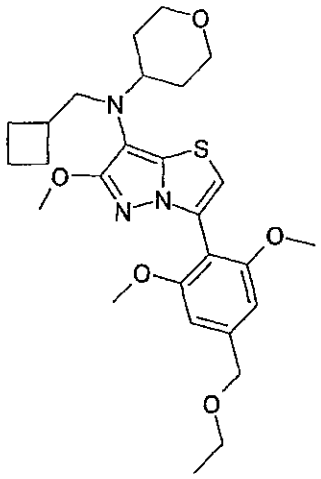
After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/1 then 1/1) to obtain the title compound (78.9 mg, 0.15 mmol).

^{1}H-NMR ($CDCl_3$) δ: -0.02-0.06 (m, 2H), 0.34-0.44 (m, 2H), 0.62-0.76 (m, 1H), 1.32 (t, J = 6.8 Hz, 3H), 1.24-1.37 (m, 2H), 1.54-1.70 (m, 2H), 1.80-1.90 (m, 2H), 3.10 (t, J = 7.6 Hz, 2H), 3.02-3.16 (m, 1H), 3.40 (td, J = 1.6, 11.6 Hz, 2H), 3.64 (q, J = 7.2 Hz, 2H), 3.81 (s, 6H), 3.87 (s, 3H), 3.96-4.06 (m, 2H), 4.57 (s, 2H), 6.43 (s, 1H), 6.68 (s, 2H).

[0096] Example 4 *N*-(Cyclobutylmethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 40]



To a mixture of *tert*-butyl {3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (100 mg, 0.216 mmol) and DMSO (0.5 mL) were added powdered sodium hydroxide (17.3 mg, 0.43 mmol) and (bromomethyl)cyclobutane (36.4 μL, 0.324 mmol) in that order at room temperature, and the mixture was stirred for 1 hour. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction mixture. After thoroughly shaking the mixture, the organic layer was separated and the solvent was distilled off with a nitrogen airflow.

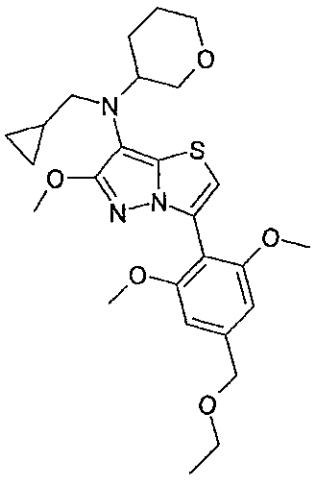
Dichloromethane (0.6 mL) was added to the resulting residue, trifluoroacetic acid (0.3 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the mixture was then distilled off with a nitrogen airflow. THF (1 mL) was added to the resulting residue, tetrahydro-4*H*-pyran-4-one (29.8 μL, 0.324 mmol) and sodium triacetoxyborohydride (68.7 mg, 0.324 mmol) were added in that order, and the mixture was stirred at room temperature for 1 hour. A saturated aqueous solution of sodium hydrogencarbonate was added to the mixture, and ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the solvent was distilled off with a nitrogen airflow. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 19/1 then 2.3/1) to obtain the title compound (98.9 mg, 0.192 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.30 (t, J = 4.0 Hz, 3H), 1.50-1.64 (m, 4H), 1.66-1.89 (m, 6H), 2.28-2.39 (m, 1H), 2.96-3.06 (m, 1H), 2.99 (d, J = 6.8 Hz, 2H), 3.37 (dt, J = 2.0, 12.0 Hz, 2H), 3.62 (q, J = 7.0 Hz, 2H), 3.77 (s, 6H), 3.85 (s, 3H), 3.93-4.00 (m, 2H),

4.54 (s, 2H), 6.40 (s, 1H), 6.65 (s, 2H).

[0097] Example 5 *N*-(Cyclopropylmethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 41]



To a mixture of *tert*-butyl {3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (120 mg, 0.259 mmol) and DMSO (0.8 mL) were added powdered sodium hydroxide (20.8 mg, 0.516 mmol) and cyclopropylmethyl bromide (37.7 μL, 0.389 mmol) at room temperature, and the mixture was stirred for 1 hour. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction mixture. After thoroughly shaking the mixture, the organic layer was separated and the solvent was distilled off with a nitrogen airflow.

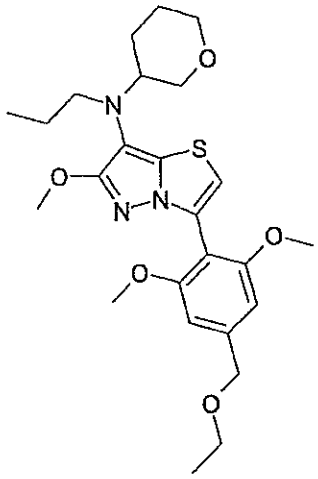
Dichloromethane (0.6 mL) was added to the resulting residue, trifluoroacetic acid (0.3 mL) was further added, and the mixture was stirred at room temperature for 1 hour. The solvent in the mixture was then distilled off with a nitrogen airflow. THF (1 mL) was then added to the resulting residue, dihydro-2*H*-pyran-3(4H)-one (38.9 mg, 0.389 mmol) and sodium triacetoxyborohydride (82.4 mg, 0.389 mmol) were added in that order, and the mixture was stirred at room temperature for 1 hour. A saturated aqueous solution of sodium hydrogencarbonate was added to the mixture, and ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the solvent was distilled off with a nitrogen airflow. The residue was purified by silica gel

column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 19/1 then 2.3/1) to obtain the title compound (93.8 mg, 0.187 mmol).

^{1}H-NMR ($CDCl_3$) δ: -0.02-0.05 (m, 2H), 0.28-0.37 (m, 2H), 0.77-0.91 (m, 1H), 1.23-1.33 (m, 1H), 1.30 (t, J = 7.0 Hz, 3H), 1.33-1.46 (m, 1H), 1.58-1.72 (m, 1H), 2.06 (br.d, J = 12.0 Hz, 1H), 2.82-2.94 (m, 2H), 3.09-3.24 (m, 3H), 3.62 (q, J = 7.0 Hz, 2H), 3.73-3.89 (m, 1H), 3.78 (s, 6H), 3.86 (s, 3H), 4.08 (br.d, J = 9.2 Hz, 1H), 4.54 (s, 2H), 6.42 (s, 1H), 6.66 (s, 2H).

[0098] Example 6 3-[4-(Ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 42]



To a mixture of *tert*-butyl {3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (120 mg, 0.259 mmol) and DMSO (0.8 mL) were added powdered sodium hydroxide (20.8 mg, 0.516 mmol) and 1-iodopropane (37.9 μL, 0.389 mmol) in that order at room temperature, and the mixture was stirred for 1 hour. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction mixture. After thoroughly shaking the mixture, the organic layer was separated and the solvent was distilled off with a nitrogen airflow.

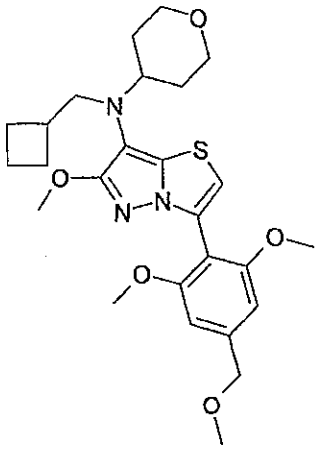
Dichloromethane (0.6 mL) was added to the resulting residue, trifluoroacetic acid (0.3 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the mixture was then distilled off with a nitrogen airflow. THF (1 mL) was then added to the resulting residue, dihydro-2*H*-pyran-3(4H)-one (38.9 mg, 0.389 mmol) and sodium triacetoxyborohydride (82.4

mg, 0.389 mmol) were added in that order, and the mixture was stirred at room temperature for 1 hour. A saturated aqueous solution of sodium hydrogencarbonate was added to the mixture, and ethyl acetate was further added. After thoroughly shaking the mixture, the organic layer was separated and the solvent was distilled off under a nitrogen stream. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 19/1 then 2.3/1) to obtain the title compound (83.6 mg, 0.171 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.86 (t, J = 7.2 Hz, 3H), 1.26-1.57 (m, 3H), 1.30 (t, J = 7.0 Hz, 3H), 1.59-1.68 (m, 2H), 2.02-2.10 (m, 1H), 2.94 (t, J = 7.4 Hz, 2H), 3.04 (tt, J = 4.0, 10.8 Hz, 1H), 3.14-3.24 (m, 2H), 3.62 (q, J = 7.0 Hz, 2H), 3.72-3.88 (m, 1H), 3.79 (s, 6H), 3.85 (s, 3H), 4.04-4.11 (m, 1H), 4.54 (s, 2H), 6.42 (s, 1H), 6.66 (s, 2H).

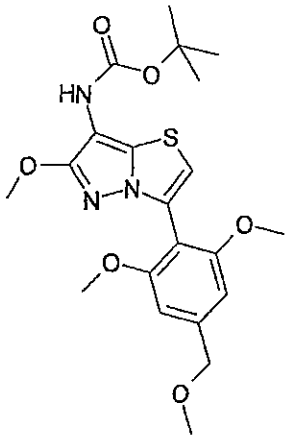
[0099] Example 7 *N*-(Cyclobutylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 43]



[0100] (7a) *tert*-Butyl {3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate

[Chemical Formula 44]



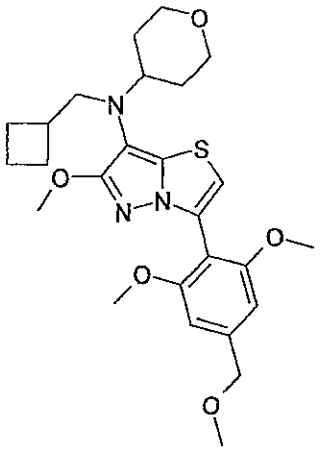
To a mixture of *tert*-butyl (3-bromo-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate (998 mg, 2.87 mmol), DME (107 mL) and water (36 mL) were added 2,6-dimethoxy-4-(methoxymethyl)phenylboric acid (Production Example 29 of WO 04/03782) (973 mg, 4.31 mmol), potassium carbonate (791 mg, 5.74 mmol), triphenylphosphine (374 mg, 1.43 mmol) and palladium acetate (64.5 mg, 0.285 mmol) in that order, and the mixture was stirred at 90°C (internal temperature) for 1.5 hours. Water was added to the mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/1 then 1/1) to obtain the title compound (1.22 g, 2.71 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 9H), 3.46 (s, 3H), 3.75 (s, 6H), 3.87 (s, 3H), 4.49 (s, 2H), 6.09 (br.s, 1H), 6.43 (s, 1H), 6.63 (s, 2H).

[0101] (7b) *N*-(Cyclobutylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 45]



Sodium hydride (60% dispersion in oil: 34.5 mg, 0.863 mmol) was added to a mixture of *tert*-butyl {3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (300 mg, 0.664 mmol) and DMF (6 mL) at room temperature, and the mixture was stirred for 30 minutes. To this mixture was added (bromomethyl)cyclobutane (97.0 μL, 0.863 mmol), and stirring was continued for 2 hours and 40 minutes. Water was added to the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Dichloromethane (10 mL) was then added to the resulting residue, trifluoroacetic acid (4 mL) was added, and the mixture was stirred at room temperature for 1 hour and 20 minutes. The solvent in the filtrate was distilled off under reduced pressure.

THF (30 mL) was then added to the resulting residue, tetrahydro-4*H*-pyran-4-one (123 μL, 1.33 mmol) and sodium triacetoxyborohydride (282 mg, 1.33 mmol) were added in that order, and the mixture was stirred at room temperature for 2 hours and 50 minutes.

A saturated aqueous solution of sodium hydrogencarbonate was added to the mixture while cooling on ice, and ethyl acetate was added.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium

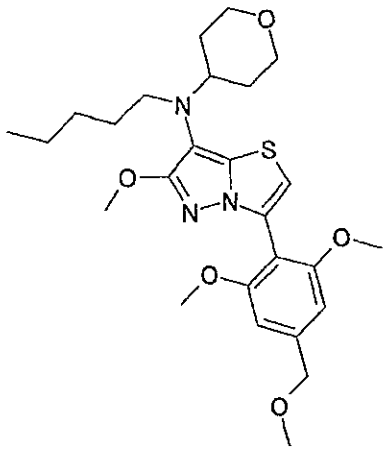
sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 9/1 then 3/2) to obtain the title compound (237 mg, 0.472 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.50-1.64 (m, 4H), 1.68-1.89 (m, 6H), 2.29-2.39 (m, 1H), 2.99 (d, J = 7.2 Hz, 2H), 2.97-3.05 (m, 1H), 3.33-3.41 (m, 2H), 3.47 (s, 3H), 3.78 (s, 6H), 3.85 (s, 3H), 3.93-4.01 (m, 2H), 4.50 (s, 2H), 6.41 (s, 1H), 6.64 (s, 2H).

[0102] Example 8 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-pentyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 46]



Sodium hydride (60% dispersion in oil: 11.6 mg, 0.289 mmol) was added to a mixture of *tert*-butyl {3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (100 mg, 0.222 mmol) and DMF (2 mL) at room temperature, and the mixture was stirred for 30 minutes. After then adding 1-bromopentane (35.8 μL, 0.289 mmol) to the mixture, stirring was continued for 30 minutes. Water was added to the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Dichloromethane (5 mL) was then added to the resulting residue,

trifluoroacetic acid (2 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the filtrate was distilled off under reduced pressure.

THF (10 mL) was then added to the resulting residue, tetrahydro-4*H*-pyran-4-one (40.8 μL, 0.444 mmol) and sodium triacetoxyborohydride (94.1 mg, 0.444 mmol) were added in that order, and the mixture was stirred at room temperature for 1 hour. A saturated aqueous solution of sodium hydrogencarbonate was added to the mixture while cooling on ice, and ethyl acetate was added.

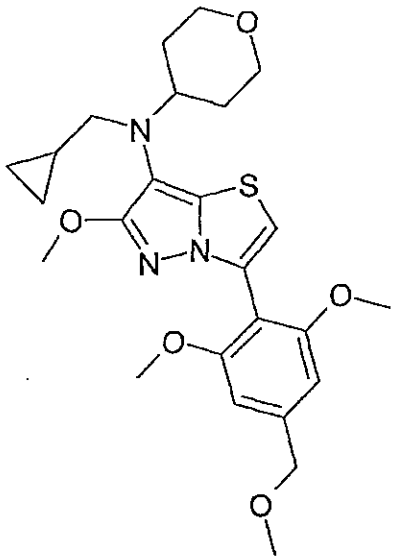
After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 9/1 then 3/2) to obtain the title compound (83.3 mg, 0.17 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.85 (t, J = 6.8 Hz, 3H), 1.22-1.32 (m, 4H), 1.32-1.41 (m, 2H), 1.53-1.65 (m, 2H), 1.78-1.86 (m, 2H), 2.97 (dd, J = 7.2, 7.6 Hz, 2H), 3.00-3.10 (m, 1H), 3.33-3.43 (m, 2H), 3.47 (s, 3H), 3.79 (s, 6H), 3.86 (s, 3H), 3.94-4.02 (m, 2H), 4.50 (s, 2H), 6.42 (s, 1H), 6.65 (s, 2H).

[0103] Example 9 *N*-(Cyclopropylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 47]



Sodium hydride (60% dispersion in oil: 9.28 mg, 0.232 mmol) was added to a mixture of *tert*-butyl {3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (80 mg, 0.178 mmol) and DMF (5 mL) at room temperature, and the mixture was stirred for 30 minutes. After then adding bromomethylcyclopropane (22.6 μL, 0.232 mmol) to the mixture, stirring was continued for 30 minutes. Water was added to the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Dichloromethane (5 mL) was added to the resulting residue, trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the filtrate was distilled off under reduced pressure.

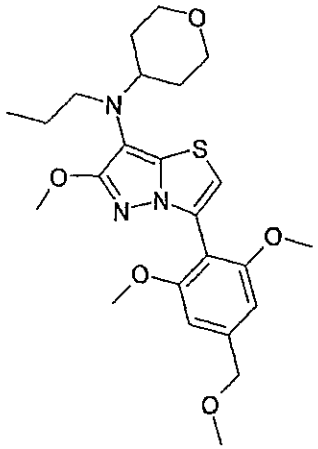
After then adding methanol (6 mL), and then tetrahydro-4*H*-pyran-4-one (34.8 μL, 0.356 mmol), acetic acid (1 mL) and α-picolineborane (38.1 mg, 0.356 mmol) in that order to the obtained residue, the mixture was stirred for 1 hour at room temperature. To this mixture was added aqueous 5N sodium hydroxide to approximate neutral pH of the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium

sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/1) to obtain the title compound (62.4 mg, 0.128 mmol).

^{1}H-NMR ($CDCl_3$) δ: -0.02-0.06 (m, 2H), 0.29-0.40 (m, 2H), 0.78-0.92 (m, 1H), 1.50-1.66 (m, 2H), 1.78-1.88 (m, 2H), 2.88 (d, J = 6.8 Hz, 2H), 3.10-3.22 (m, 1H), 3.39 (td, J = 1.6, 11.6 Hz, 2H), 3.47 (s, 3H), 3.79 (s, 6H), 3.87 (s, 3H), 3.92-4.03 (m, 2H), 4.50 (s, 2H), 6.41 (s, 1H), 6.65 (s, 2H).

[0104] Example 10 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 48]



Sodium hydride (60% dispersion in oil: 6.73 mg, 0.168 mmol) was added to a mixture of *tert*-butyl {3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (58 mg, 0.13 mmol) and DMF (4 mL) at room temperature, and the mixture was stirred for 30 minutes. After then adding 1-iodopropane (16.4 μL, 0.168 mmol) to the mixture, stirring was continued for 30 minutes. Water was added to the mixture while cooling on ice, and then ethyl acetate was further added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Dichloromethane (5 mL) was added to the resulting residue, trifluoroacetic acid (1 mL) was further added, and the mixture was stirred at room temperature for

1 hour. The solvent in the filtrate was distilled off under reduced pressure.

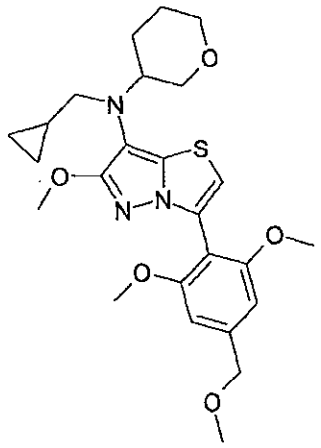
After then adding methanol (6 mL), and then tetrahydro-4*H*-pyran-4-one (25.4 μL, 0.26 mmol), acetic acid (1 mL) and α-picolineborane (27.8 mg, 0.26 mmol) in that order to the obtained residue, the mixture was stirred for 1 hour at room temperature. To this mixture there was added aqueous 5N sodium hydroxide to approximate neutral pH of the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/1) to obtain the title compound (50.0 mg, 0.105 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, J = 7.2 Hz, 3H), 1.32-1.45 (m, 2H), 1.53-1.66 (m, 2H), 1.78-1.88 (m, 2H), 2.90-2.99 (m, 2H), 3.00-3.12 (m, 1H), 3.38 (td, J = 2.0, 12.0 Hz, 2H), 3.47 (s, 3H), 3.79 (s, 6H), 3.86 (s, 3H), 3.94-4.03 (m, 2H), 4.50 (s, 2H), 6.42 (s, 1H), 6.65 (s, 2H).

[0105] Example 11 *N*-(Cyclopropylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 49]



To a mixture of *tert*-butyl {3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (120 mg, 0.267 mmol) and

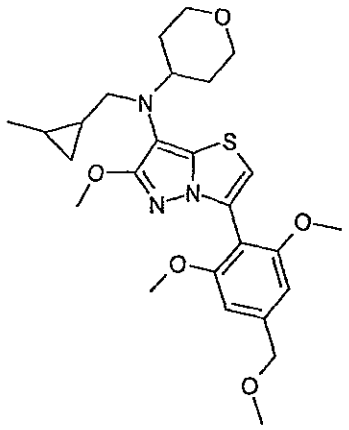
DMSO (0.8 mL) were added powdered sodium hydroxide (21.4 mg, 0.534 mmol) and cyclopropylmethyl bromide (38.8 μL, 0.401 mmol) at room temperature, and the mixture was stirred for 1 hour. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction mixture. After thoroughly shaking the mixture, the organic layer was separated and the solvent was distilled off with a nitrogen airflow.

Dichloromethane (0.6 mL) was added to the resulting residue, trifluoroacetic acid (0.3 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the mixture was then distilled off with a nitrogen airflow. THF (1 mL) was added to the resulting residue, dihydro-2*H*-pyran-3(4H)-one (40.1 mg, 0.401 mmol) and sodium triacetoxyborohydride (84.9 mg, 0.401 mmol) were added in that order, and the mixture was stirred at room temperature for 1 hour. A saturated aqueous solution of sodium hydrogencarbonate was added to the mixture, and ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the solvent was distilled off under a nitrogen stream. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 19/1 then 2.3/1) to obtain the title compound (96.1 mg, 0.197 mmol).

^{1}H-NMR ($CDCl_3$) δ: -0.02-0.05 (m, 2H), 0.30-0.37 (m, 2H), 0.77-0.88 (m, 1H), 1.34-1.46 (m, 1H), 1.60-1.69 (m, 2H), 2.02-2.10 (m, 1H), 2.86 (dd, J = 6.4, 12.8 Hz, 1H), 2.90 (dd, J = 6.4, 12.8 Hz, 1H), 3.08-3.24 (m, 3H), 3.47 (s, 3H), 3.75-3.88 (m, 1H), 3.78 (s, 6H), 3.86 (s, 3H), 4.05-4.11 (m, 1H), 4.50 (s, 2H), 6.43 (s, 1H), 6.65 (s, 2H).

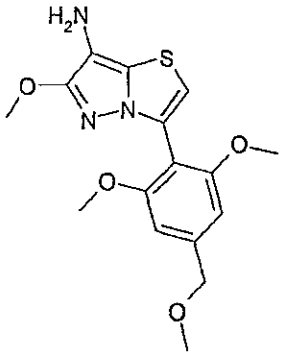
[0106] Example 12 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-[(2-methylcyclopropyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 50]



[0107] (12a) 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 51]



To a mixture of *tert*-butyl {3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate (1.37 g, 3.05 mmol) and ethyl acetate (10 mL) was added a 4M solution of HCl in ethyl acetate (20 mL), and the mixture was stirred at room temperature for 3 hours. The solvent in the mixture was distilled off under reduced pressure, and then ethyl acetate was added to the obtained residue and a saturated aqueous solution of sodium carbonate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

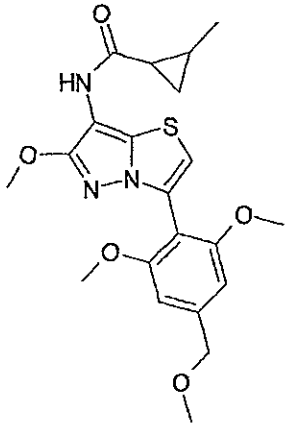
The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. To the residue there was added a mixture of *n*-heptane and ethyl acetate, and the precipitated solid was collected by filtration and dried under reduced pressure to obtain the title compound (836.6 mg, 2.39 mmol).

^{1}H-NMR ($CDCl_3$) δ: 2.60 (br.s, 2H), 3.46 (s, 3H), 3.77 (s, 6H), 3.89 (s, 3H), 4.50 (s,

2H), 6.40 (s, 1H), 6.64 (s, 2H).

[0108] (12b) *N*-{3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}-2-methylcyclopropanecarboxamide

[Chemical Formula 52]



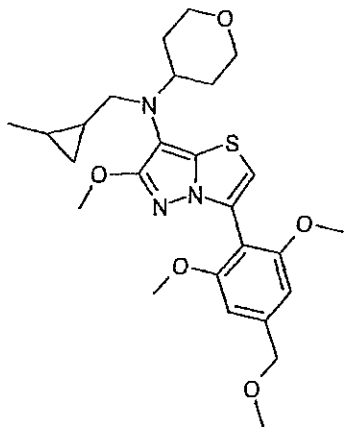
To a mixture of WSCD (104 mg, 0.67 mmol) and DMF (5 mL) was added 1-hydroxybenzotriazole (90.4 mg, 0.67 mmol), and then 3-(2,6-dimethoxy-4-methoxymethylphenyl)-6-methoxypyrazolo[5,1-b]thiazol-7-ylamine (200 mg, 0.57 mmol) and 2-methylcyclopropanecarboxylic acid (60.8 μL, 0.62 mmol) were added in that order and the mixture was stirred at room temperature for 14 hours. Water was added to the reaction mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by (NH)silica gel chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/1) to obtain the title compound (215.9 mg, 0.50 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.65-0.68 (m, 1H), 1.14 (d, J = 6.0 Hz, 3H), 1.21-1.31 (m, 2H), 1.46-1.52 (m, 1H), 3.46 (s, 3H), 3.75 (s, 6H), 3.90 (s, 3H), 4.49 (s, 2H), 6.43 (s, 1H), 6.62 (s, 2H), 7.14 (br.s, 1H).

[0109] (12c) 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-[(2-methylcyclopropyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 53]



To a mixture of *N*-{3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl}-2-methylcyclopropanecarboxamide (100 mg, 0.23 mmol) and THF (2 mL) was added a solution of borane in tetrahydrofuran (0.99 M, 609 μL, 0.60 mmol), and the mixture was stirred at 55°C for 2 hours. Water was added to the reaction mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

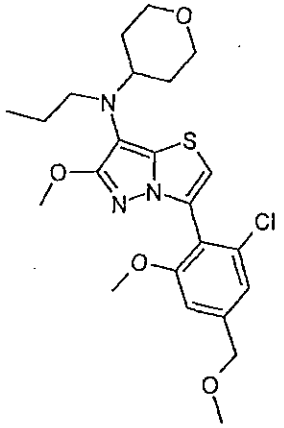
The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. To a mixture of the obtained residue and THF (1.5 mL) were added trifluoroacetic acid (150 μL), and then tetrahydro-4H-pyran-4-one (32 μL, 0.35 mmol) and sodium triacetoxyborohydride (73.8 mg, 0.35 mmol) in that order, and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by (NH)silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 4/1). The fractions containing the target substance were collected, the solvent was distilled off under reduced pressure, and then a mixture of *n*-heptane and diisopropyl ether was added to the resulting residue. The precipitated solid was collected by filtration, and the obtained residue was washed with a small amount of *n*-heptane and then dried under reduced pressure to obtain the title compound (43.7 mg, 0.09 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.06-0.10 (m, 1H), 0.15-0.19 (m, 1H), 0.26-0.36 (m, 1H), 0.47-0.58 (m, 1H), 0.79 (d, J = 5.6 Hz, 3H), 1.50-1.68 (m, 2H), 1.78-1.89 (m, 2H), 2.68 (dd, J = 8.0, 12.0 Hz, 1H), 3.04-3.18 (m, 2H), 3.33-3.46 (m, 2H), 3.48 (s, 3H), 3.79 (s, 6H), 3.87 (s, 3H), 3.94-4.03 (m, 2H), 4.52 (s, 2H), 6.41 (s, 1H), 6.66 (s, 2H).

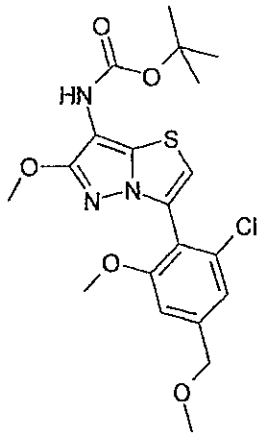
[0110] Example 13 3-[2-Chloro-6-methoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 54]



[0111] (13a) *tert*-Butyl {3-[2-chloro-6-methoxy-4-(methoxymethyl)phenyl]-6-methoxy-pyrazolo[5,1-*b*][1,3]thiazol-7-yl}carbamate

[Chemical Formula 55]



To a mixture of *tert*-butyl (3-bromo-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate (500 mg, 1.44 mmol), toluene (8 mL) and ethanol (4 mL) were added [2-chloro-6-methoxy-4-(methoxymethyl)phenyl]boronic acid (498 mg, 2.16

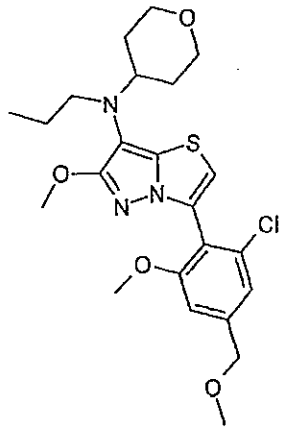
mmol), a 1M aqueous solution of sodium carbonate (2.88 mL, 2.88 mmol) and tetrakis(triphenylphosphine)palladium(0) (166 mg, 0.14 mmol) in that order, and the mixture was stirred at 110°C for 6 hours. Water was added to the mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by (NH)silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 3/1 then 2/1) to obtain the title compound (349 mg, 0.77 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 9H), 3.46 (s, 3H), 3.76 (s, 3H), 3.87 (s, 3H), 4.48 (s, 2H), 6.13 (br.s, 1H), 6.48 (s, 1H), 6.91 (s, 1H), 7.08 (s, 1H).

[0112] (13b) 3-[2-Chloro-6-methoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 56]



To a mixture of *tert*-butyl {3-[2-chloro-6-methoxy-4-(methoxymethyl)phenyl]-6-methoxy-pyrazolo[5,1-b][1,3]thiazol-7-yl}carbamate (148 mg, 0.33 mmol) and DMF (4 mL) was added sodium hydride (60% dispersion in oil: 17 mg, 0.42 mmol) at room temperature, and the mixture was stirred for 10 minutes. After then adding 1-iodobutane (41.3 μL, 0.42 mmol) to the mixture, stirring was continued for 2 hours. Water was added to the reaction mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate.

The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

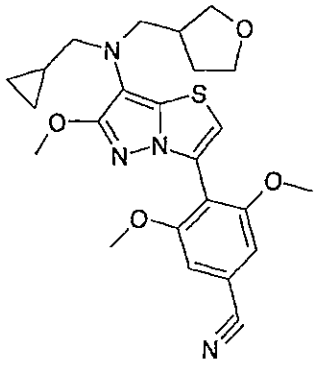
Dichloromethane (2 mL) was added to the resulting residue, trifluoroacetic acid (2 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the filtrate was distilled off under reduced pressure.

THF (4 mL) was then added to the resulting residue, tetrahydro-4*H*-pyran-4-one (59.9 μL, 0.65 mmol) and sodium triacetoxyborohydride (138 mg, 0.65 mmol) were added in that order, and the mixture was stirred at room temperature for 14 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture, and ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by (NH)silica gel chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 4/1 then 3/1) to obtain the title compound (94.8 mg, 0.20 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, J = 7.2 Hz, 3H), 1.32-1.44 (m, 2H), 1.52-1.66 (m, 2H), 1.79-1.86 (m, 2H), 2.92-2.97 (m, 2H), 3.02-3.11 (m, 1H), 3.34-3.41 (m, 2H), 3.47 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 3.96-4.02 (m, 2H), 4.49 (s, 2H), 6.46 (s, 1H), 6.93 (br.s, 1H), 7.09 (br.s, 1H).

[0113] Example 14 4-{7-[(Cyclopropylmethyl)(tetrahydrofuran-3-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile

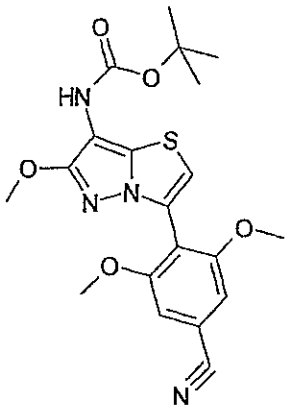
[Chemical Formula 57]



[0114] (14a) *tert*-Butyl [3-(4-cyano-2,6-dimethoxyphenyl)-6-

methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl]carbamate

[Chemical Formula 58]

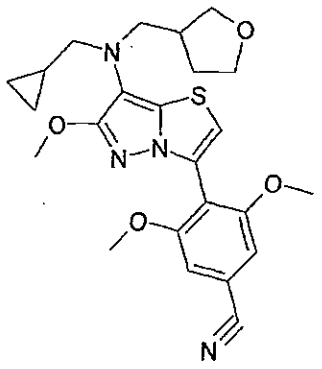


To a mixture of *tert*-butyl (3-bromo-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate (461 mg, 1.33 mmol), DME (49 mL) and water (16 mL) were added (4-cyano-2,6-dimethoxyphenyl)boronic acid (412 mg, 2.00 mmol), potassium carbonate (366 mg, 2.66 mmol), triphenylphosphine (174 mg, 0.659 mmol) and palladium acetate (29.8 mg, 0.132 mmol) in that order, and the mixture was stirred at 90°C (internal temperature) for 2 hours. Water was added to the mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/1 then 1/1) to obtain the title compound (296 mg, 0.688 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 9H), 3.78 (s, 6H), 3.87 (s, 3H), 6.11 (br.s, 1H), 6.50 (s, 1H), 6.91 (s, 2H).

[0115] (14b) 4-{7-[(Cyclopropylmethyl)(tetrahydrofuran-3-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile

[Chemical Formula 59]



To a mixture of *tert*-butyl [3-(4-cyano-2,6-dimethoxyphenyl)-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl]carbamate (66 mg, 0.153 mmol) and DMF (4 mL) were added sodium hydride (60% dispersion in oil: 7.96 mg, 0.199 mmol) and cyclopropylmethyl bromide (19.3 μL, 0.199 mmol) in that order at room temperature, and the mixture was stirred for 1 hour. Water was added to the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Dichloromethane (6 mL) was added to the residue, trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the filtrate was distilled off under reduced pressure.

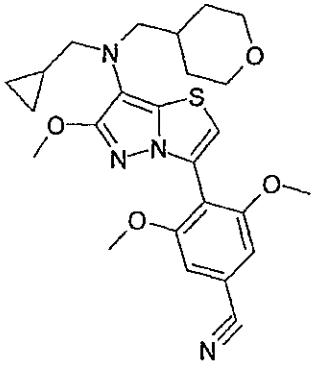
After then adding methanol (6 mL), and then tetrahydrofuran-3-carboxaldehyde (55.4 μL, 0.306 mmol), acetic acid (1 mL) and α-picolineborane (32.7 mg, 0.306 mmol) in that order to the obtained residue, the mixture was stirred for 1 hour at room temperature. To this mixture was added aqueous 5N sodium hydroxide to approximate neutral pH of the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/1 then 1/1) to obtain the title compound (53.9 mg, 0.115 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.01-0.10 (m, 2H), 0.36-0.46 (m, 2H), 0.83-0.96 (m, 1H),

1.58-1.71 (m, 1H), 1.90-2.03 (m, 1H), 2.26-2.40 (m, 1H), 2.81 (d, J = 6.4 Hz, 2H), 2.95 (dd, J = 8.4, 12.0 Hz, 1H), 3.07 (dd, J = 6.8, 12.0 Hz, 1H), 3.56 (dd, J = 6.0, 8.4 Hz, 1H), 3.65-3.74 (m, 1H), 3.81 (s, 6H), 3.86 (s, 3H), 3.76-3.88 (m, 2H), 6.49 (s, 1H), 6.92 (s, 2H).

[0116] Example 15 4-{7-[(Cyclopropylmethyl)(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile

[Chemical Formula 60]



To a mixture of *tert*-butyl [3-(4-cyano-2,6-dimethoxyphenyl)-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl]carbamate (90 mg, 0.21 mmol) and DMSO (0.8 mL) were added powdered sodium hydroxide (16.8 mg, 0.42 mmol) and cyclopropylmethyl bromide (30.7 μL, 0.317 mmol) at room temperature, and the mixture was stirred for 1 hour. A saturated aqueous solution of ammonium chloride and ethyl acetate were then added to the reaction mixture. After thoroughly shaking the mixture, the organic layer was separated and the solvent was distilled off with a nitrogen airflow.

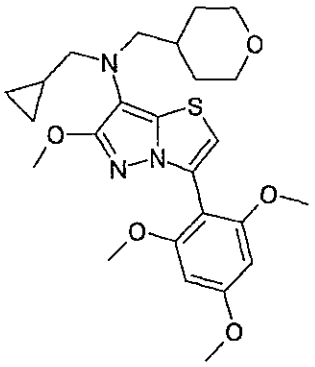
Dichloromethane (0.6 mL) was added to the resulting residue, trifluoroacetic acid (0.2 mL) was added and the mixture was stirred at room temperature for 2 hours. The solvent in the mixture was then distilled off with a nitrogen airflow. THF (1 mL) was then added to the resulting residue, tetrahydro-2*H*-pyran-4-carbaldehyde (36 mg, 0.315 mmol) and sodium triacetoxyborohydride (66.8 mg, 0.315 mmol) were added in that order, and the mixture was stirred at room temperature for 2 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the mixture, and ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the solvent

was distilled off with a nitrogen airflow. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/0 then 3/2) to obtain the title compound (71.3 mg, 0.148 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.00-0.06 (m, 2H), 0.36-0.44 (m, 2H), 0.84-0.94 (m, 1H), 1.21-1.34 (m, 2H), 1.54-1.67 (m, 1H), 1.71-1.80 (m, 2H), 2.80 (d, J = 6.8 Hz, 2H), 2.89 (d, J = 7.2 Hz, 2H), 3.33 (dt, J = 1.6, 11.6 Hz, 2H), 3.82 (s, 6H), 3.86 (s, 3H), 3.90-3.97 (m, 2H), 6.49 (s, 1H), 6.93 (s, 2H).

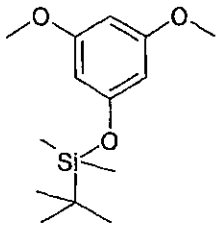
[0117] Example 16 *N*-(Cyclopropylmethyl)-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-3-(2,4,6-trimethoxyphenyl)-pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 61]



[0118] (16a) *tert*-Butyl(3,5-dimethoxyphenoxy)dimethylsilane

[Chemical Formula 62]



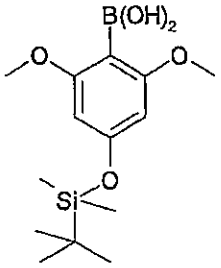
To a mixture of 3,5-dimethoxyphenol (3.00 g, 19.5 mmol) and DMF (45 mL) were added imidazole (2.66 g, 39.0 mmol) and *tert*-butyldimethylchlorosilane (2.94 g, 19.5 mmol) in that order, and the mixture was stirred for 19.5 hours at room temperature. Water was added to the reaction mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column

chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 9/1) to obtain the title compound (4.98 g, 18.6 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.21 (s, 6H), 0.98 (s, 9H), 3.75 (s, 6H), 6.02 (d, J = 2.4 Hz, 2H), 6.11 (t, J = 2.4 Hz, 1H).

[0119] (16b) (4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,6-dimethoxyphenyl)boronic acid

[Chemical Formula 63]

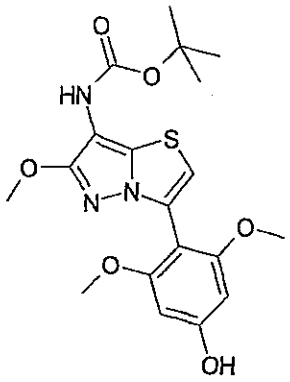


To a mixture of *tert*-butyl(3,5-dimethoxyphenoxy)dimethylsilane (4.97 g, 18.5 mmol) and THF (50.0 mL) were added *N,N,N',N'*-tetramethylethylenediamine (3.35 mL, 22.2 mmol) and *n*-butyllithium (2.77 M solution in *n*-hexane: 8.01 mL, 22.2 mmol) in that order at room temperature, and the mixture was stirred for 1 hour at room temperature. The mixture was then cooled to -78°C (internal temperature), and then trimethyl borate (2.48 mL, 22.2 mmol) was added and the temperature was raised to room temperature while stirring. A saturated aqueous solution of ammonium chloride was added to the reaction mixture and then ethyl acetate was added, while cooling on ice. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 4/1) to obtain the title compound (3.50 g, 11.2 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.25 (s, 6H), 1.00 (s, 9H), 3.86 (s, 6H), 6.11 (s, 2H), 7.04 (s, 2H).

[0120] (16c) *tert*-Butyl [3-(4-hydroxy-2,6-dimethoxyphenyl)-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl]carbamate

[Chemical Formula 64]

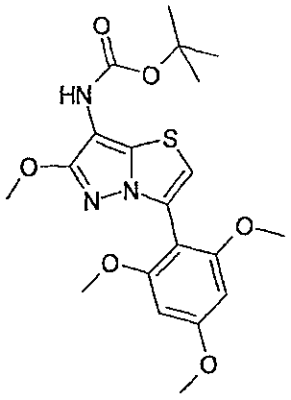


To a mixture of *tert*-butyl (3-bromo-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate (400 mg, 1.15 mmol), 1,4-dioxane (26.7 mL) and water (13.3 mL) were added (4-{[*tert*-butyl(dimethyl)silyl]oxy}-2,6-dimethoxyphenyl)boronic acid (647 mg, 2.07 mmol), potassium carbonate (318 mg, 2.29 mmol) and tetrakis(triphenylphosphine)palladium(0) (133 mg, 0.115 mmol) in that order, and the mixture was stirred for 1 hour at 110°C (internal temperature). Water was added to the mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/1) to obtain the title compound (224 mg, 0.53 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.54 (s, 9H), 3.61 (s, 6H), 3.99 (s, 3H), 5.93 (s, 2H), 6.10 (br.s, 1H), 6.38 (s, 1H).

[0121] (16d) *tert*-Butyl [6-methoxy-3-(2,4,6-trimethoxyphenyl)pyrazolo[5,1-*b*][1,3]thiazol-7-yl)]carbamate

[Chemical Formula 65]

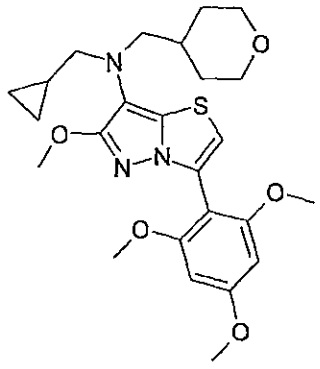


To a mixture of *tert*-butyl [3-(4-hydroxy-2,6-dimethoxyphenyl)-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)]carbamate (224 mg, 0.531 mmol) and DMF (5.00 mL) were added potassium carbonate (117 mg, 0.85 mmol) and iodomethane (52.9 μL, 0.85 mmol) in that order at room temperature, and the mixture was stirred for 14.5 hours. Water was added to the reaction mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was then filtered, and the solvent in the filtrate was distilled off under reduced pressure to obtain the title compound (231 mg, 0.53 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 9H), 3.73 (s, 6H), 3.86 (s, 3H), 3.89 (s, 3H), 6.10 (br.s, 1H), 6.20 (s, 2H), 6.40 (s, 1H).

[0122] (16e) *N*-(Cyclopropylmethyl)-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-3-(2,4,6-trimethoxyphenyl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 66]



To a mixture of *tert*-butyl [6-methoxy-3-(2,4,6-

trimethoxyphenyl)pyrazolo[5,1-*b*][1,3]thiazol-7-yl)]carbamate (112 mg, 0.256 mmol) and DMF (2.5 mL) was added sodium hydride (60% dispersion in oil: 16.0 mg, 0.333 mmol) at room temperature, and the mixture was stirred for 30 minutes. After adding cyclopropylmethyl bromide (32.3 μL, 0.333 mmol) to the mixture, stirring was continued for 40 minutes. Water was added to the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

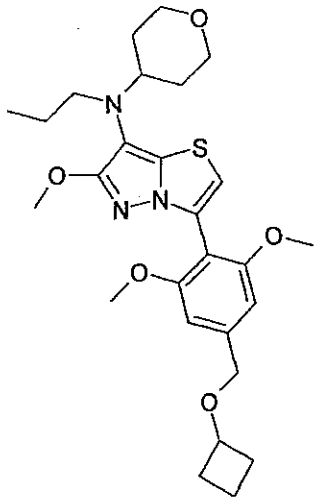
Dichloromethane (2.5 mL) was added to the resulting residue, trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 1 hour and 20 minutes. The solvent in the filtrate was distilled off under reduced pressure.

THF (4 mL) was then added to the resulting residue, tetrahydro-2*H*-pyran-4-carbaldehyde (29.4 mg, 0.257 mmol) and sodium triacetoxyborohydride (54.5 mg, 0.257 mmol) were added in that order, and the mixture was stirred at room temperature for 2 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the mixture while cooling on ice, and ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 9/1 then 3/2) to obtain the title compound (75.0 mg, 0.16 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.00-0.06 (m, 2H), 0.35-0.43 (m, 2H), 0.87-0.97 (m, 1H), 1.20-1.36 (m, 2H), 1.55-1.69 (m, 1H), 1.71-1.81 (m, 2H), 2.80 (dd, J = 6.4 Hz, 2H), 2.89 (d, J = 6.8 Hz, 2H), 3.27-3.39 (m, 2H), 3.76 (s, 6H), 3.87 (s, 3H), 3.88 (s, 3H), 3.88-3.98 (m, 2H), 6.23 (s, 2H), 6.37 (s, 1H).

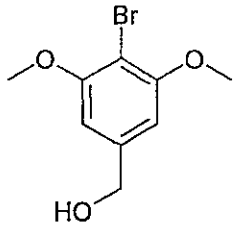
[0123] Example 17 3-{4-[(Cyclobutyloxy)methyl]-2,6-dimethoxyphenyl}-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 67]



[0124] (17a) (4-Bromo-3,5-dimethoxyphenyl)methanol

[Chemical Formula 68]

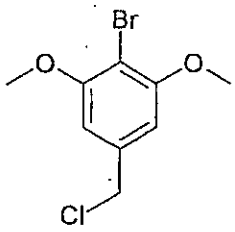


To a mixture of 4-bromo-3,5-dimethoxybenzoic acid (50.0 g, 192 mmol) and THF (1 L) was added borane-methyl sulfide (27.1 mL, 286 mmol) while cooling on ice, and the mixture was heated to reflux for 1 hour. Water was slowly added to the mixture while cooling on ice, and then the solvent in the mixture was distilled off under reduced pressure. Water and ethyl acetate were added to the residue. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was then filtered, and the solvent in the filtrate was distilled off under reduced pressure to obtain the title compound (47.3 g, 191 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.80 (s, 1H), 3.91 (s, 6H), 4.68 (s, 2H), 6.60 (s, 2H).

[0125] (17b) 2-Bromo-5-(chloromethyl)-1,3-dimethoxybenzene

[Chemical Formula 69]

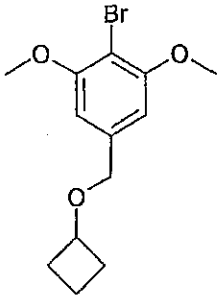


To a mixture of (4-bromo-3,5-dimethoxyphenyl)methanol (10.0 g, 40.6 mmol) and dichloromethane (100 mL) were added triethylamine (12.4 mL, 89.3 mmol) and methanesulfonyl chloride (3.46 mL, 44.7 mmol) in that order while cooling on ice, and the mixture was stirred at room temperature for 14 hours. Water was added to the mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 4/1) to obtain the title compound (2.47 g, 9.30 mmol).

^{1}H-NMR ($CDCl_3$) δ: 3.92 (s, 6H), 4.55 (s, 2H), 6.60 (s, 2H).

[0126] (17c) 2-Bromo-5-[(cyclobutyloxy)methyl]-1,3-dimethoxybenzene

[Chemical Formula 70]



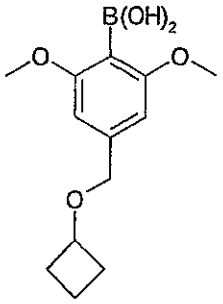
To a mixture of cyclobutyl alcohol (4.16 g, 57.7 mmol) and DMF (30 mL) was added sodium hydride (60% dispersion in oil: 2.31 g, 57.7 mmol) while cooling on ice, and the mixture was stirred at room temperature for 1 hour. To this mixture was slowly added dropwise a mixture of 2-bromo-5-(chloromethyl)-1,3-dimethoxybenzene (2.47 g, 9.3 mmol) and DMF (30 mL), and the resulting mixture was stirred at room temperature for 1 hour. Water was added to the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the

mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 4/1) to obtain the title compound (2.39 g, 7.94 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.43-1.60 (m, 1H), 1.65-1.80 (m, 1H), 1.92-2.08 (m, 2H), 2.15-2.28 (m, 2H), 3.90 (s, 6H), 3.96-4.07 (m, 1H), 4.38 (s, 2H), 6.56 (s, 2H).

[0127] (17d) {4-[(Cyclobutyloxy)methyl]-2,6-dimethoxyphenyl}boronic acid

[Chemical Formula 71]

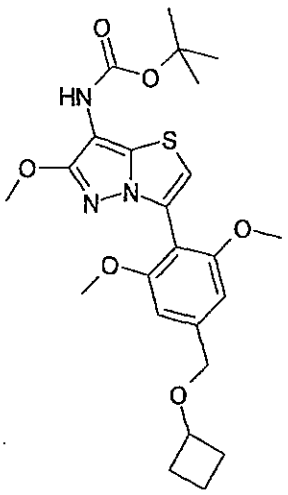


To a mixture of 2-bromo-5-[(cyclobutyloxy)methyl]-1,3-dimethoxybenzene (2.39 g, 7.94 mmol) and THF (20 mL) was added *n*-butyllithium (2.73 M solution in *n*-hexane: 3.49 mL, 9.53 mmol) at -78°C (internal temperature), and the mixture was stirred for 1 hour. After then adding trimethyl borate (1.07 mL, 9.53 mmol) to the mixture, the temperature was slowly raised to room temperature while stirring. A saturated aqueous solution of ammonium chloride was added to the reaction mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. Heptane (30 mL) was added to the residue, the precipitated solid was collected by filtration and dried under reduced pressure to obtain the title compound (905 mg, 3.40 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.45-1.60 (m, 1H), 1.67-1.80 (m, 1H), 1.94-2.08 (m, 2H), 2.18-2.30 (m, 2H), 3.92 (s, 6H), 3.96-4.07 (m, 1H), 4.41 (s, 2H), 6.61 (s, 2H), 7.18 (s, 2H).

[0128] (17e) *tert*-Butyl (3-{4-[(cyclobutyloxy)methyl]-2,6-dimethoxyphenyl}-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate

[Chemical Formula 72]

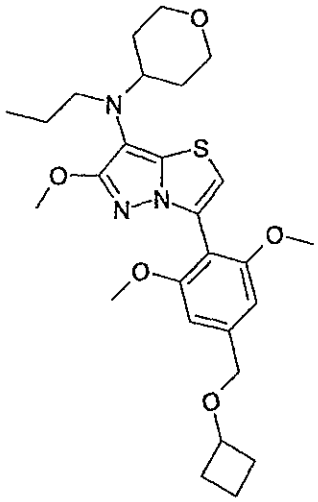


To a mixture of *tert*-butyl (3-bromo-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate (987 mg, 2.83 mmol), DME (80 mL) and water (28 mL) were added {4-[(cyclobutyloxy)methyl]-2,6-dimethoxyphenyl}boronic acid (904 mg, 3.4 mmol), potassium carbonate (785 mg, 5.68 mmol), triphenylphosphine (370 mg, 1.42 mmol) and palladium acetate (63.7 mg, 0.282 mmol) in that order, and the mixture was stirred at 90°C (internal temperature) for 3 hours. Water was added to the reaction mixture, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 2/1) to obtain the title compound (1.24 g, 2.53 mmol).

^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 9H), 1.46-1.62 (m, 1H), 1.66-1.81 (m, 1H), 1.96-2.10 (m, 2H), 2.20-2.32 (m, 2H), 3.75 (s, 6H), 3.87 (s, 3H), 4.02-4.13 (m, 1H), 4.43 (s, 2H), 6.08 (br.s, 1H), 6.41 (s, 1H), 6.62 (s, 2H).

[0129] (17f) 3-{4-[(Cyclobutyloxy)methyl]-2,6-dimethoxyphenyl}-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine

[Chemical Formula 73]



To a mixture of *tert*-butyl (3-{4-[(cyclobutyloxy)methyl]-2,6-dimethoxyphenyl}-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-7-yl)carbamate (123 mg, 0.251 mmol) and DMF (6 mL) was added sodium hydride (60% dispersion in oil: 13.0 mg, 0.326 mmol) at room temperature, and the mixture was stirred for 30 minutes. After then adding 1-iodopropane (35.4 μL, 0.326 mmol) to the mixture, stirring was continued for 30 minutes. Water was added to the mixture while cooling on ice, and then ethyl acetate was added. After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled off under reduced pressure.

Dichloromethane (6 mL) was added to the resulting residue, trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 1 hour. The solvent in the filtrate was distilled off under reduced pressure.

THF (10 mL) was then added to the resulting residue, tetrahydro-4*H*-pyran-4-one (49 μL, 0.501 mmol), acetic acid (1 mL) and sodium triacetoxyborohydride (106 mg, 0.501 mmol) were added in that order, and the mixture was stirred at room temperature for 14 hours. To this mixture there was added aqueous 5N sodium hydroxide to approximate neutral pH of the mixture while cooling on ice, and then ethyl acetate was added.

After thoroughly shaking the mixture, the organic layer was separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered, and then the solvent in the filtrate was distilled

off under reduced pressure. The residue was purified by silica gel column chromatography (mixture of *n*-heptane and ethyl acetate: *n*-heptane/ethyl acetate = 1/1) to obtain the title compound (98.0 mg, 0.19 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, J = 7.2 Hz, 3H), 1.32-1.44 (m, 2H), 1.46-1.66 (m, 3H), 1.69-1.87 (m, 3H), 1.98-2.11 (m, 2H), 2.21-2.33 (m, 2H), 2.94 (t, J = 7.2 Hz, 2H), 3.00-3.10 (m, 1H), 3.38 (td, J = 1.6, 11.6 Hz, 2H), 3.79 (s, 6H), 3.85 (s, 3H), 3.94-4.02 (m, 2H), 4.03-4.13 (m, 1H), 4.44 (s, 2H), 6.40 (s, 1H), 6.64 (s, 2H).

[0130] Example 1x *N*-Butyl-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine hydrobromide

To a mixture of *N*-butyl-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (6 mg) and methanol (1 mL) was added hydrobromic acid (8.84M, 2.0 μL), and the mixture was stirred at room temperature for 1 hour and the solvent was distilled off under reduced pressure. Methanol (1 mL) was added to the residue and the solvent was distilled off under reduced pressure. Ethyl acetate (1 mL) was added to the resultant residue and the solvent was distilled off under reduced pressure and dried to obtain the titled compound (6.0 mg).

[0131] Example 2x *N*-Butyl-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine hydrobromide

To *N*-butyl-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (1.02 g) was added acetone (2 mL) warmed by hot water, then hydrobromic acid (8.84M, 240 μL) was added, and the mixture was stirred. The solvent in the mixture was partially removed by blowing nitrogen stream, and the mixture was further stirred.

The mixture was allowed to stand at room temperature under reduced pressure for 13 hours to remove the solvent in the residue. The resultant residue was finely triturated, acetone (2 mL) and heptane (2 mL) were added, and the mixture was shaken under sonication (a bath-type sonicator) for 1 minute. The vessel was protected from light and sealed tightly, and the mixture was stirred for one day.

The precipitate in the mixture was collected by suction filtration, and

allowed to stand at room temperature under reduced pressure to remove the solvent in the residue. To the residue was added acetone (20 mL), and heptane (3 mL) was added and the mixture was stirred for several minutes. Heptane (5 mL) was added, the vessel was protected from light, and the mixture was stirred for one day. The precipitate in the mixture was collected by suction filtration, and allowed to stand at room temperature under reduced pressure to remove the solvent in the residue and the title compound (701.17 mg) was obtained.

[0132] Example 2y *N*-Butyl-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine phosphate

To *N*-butyl-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (2.99 g) were added ethanol (7 mL) warmed by hot water and phosphoric acid (14.6M, 410 μL). Heptane was added by 1 mL and the volume totaled 30 mL. The mixture was stirred for 1 hour under shading.

The precipitate in the mixture was collected by suction filtration, allowed to stand at room temperature under reduced pressure for 1 week to remove the solvent in the residue and dried by heating at 60°C for 1.5 hours to obtain the title compound (4.10 g).

[0133] Example 3x *N*-(2-Cyclopropylethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine phosphate

To a mixture of *N*-(2-cyclopropylethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (757.0 mg), ethanol (10 mL) and ethyl acetate (5 mL) was added phosphoric acid (14.6M, 101 μL). The mixture was stirred at room temperature for 5 minutes and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (856.0 mg).

[0134] Example 3y *N*-(2-Cyclopropylethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine methanesulfonate

To a mixture of *N*-(2-cyclopropylethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-

b][1,3]thiazole-7-amine (16.2 mg) and ethyl acetate (0.5 mL) was added methanesulfonic acid (2.05 μL). The mixture was stirred at room temperature for 1 hour and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (19.2 mg).

[0135] Example 3z *N*-(2-Cyclopropylethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine sulfate

To a mixture of *N*-(2-cyclopropylethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (59.6 mg), ethanol (2 mL) and ethyl acetate (1 mL) was added concentrated sulfuric acid (6.18 μL). The mixture was stirred at room temperature for 2 hours and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (66.3 mg).

[0136] Example 4x *N*-(Cyclobutylmethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine methanesulfonate

To a mixture of *N*-(cyclobutylmethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (13.4 mg) and ethyl acetate (0.5 mL) was added methanesulfonic acid (1.69 μL). The mixture was stirred at room temperature for 1 hour and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (15.9 mg).

[0137] Example 5x *N*-(Cyclopropylmethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine sulfate

To a mixture of *N*-(cyclopropylmethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (42.0 mg), ethanol (2 mL) and ethyl acetate (1 mL) was added concentrated sulfuric acid (4.46 μL). The mixture was stirred at room temperature for 2 hours and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (45.7 mg).

[0138] Example 6x 3-[4-(Ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine sulfate

To a mixture of 3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (8.1 mg) and ethanol (2 mL) was added concentrated sulfuric acid (0.88 μL). The mixture was stirred at room temperature for 2 hours and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (9.8 mg).

[0139] Example 7x *N*-(Cyclobutylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine sulfate

To a mixture of *N*-(cyclobutylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (99.0 mg), ethanol (2 mL) and ethyl acetate (1 mL) was added concentrated sulfuric acid (10.5 μL). The mixture was stirred at room temperature for 2 hours and the solvent was distilled off under reduced pressure and dried to obtain the title compound (120.4 mg).

[0140] Example 7y *N*-(Cyclobutylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine methanesulfonate

To a mixture of *N*-(cyclobutylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (26.2 mg) and ethyl acetate (1.0 mL) was added methanesulfonic acid (3.40 μL). The mixture was stirred at room temperature for 1 hour and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (31.2 mg).

[0141] Example 8x 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-pentyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine methanesulfonate

To a mixture of 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-pentyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (12.2 mg) and ethyl acetate (0.5 mL) was added methanesulfonic acid (1.58 μL). The mixture was stirred at room temperature for 1 hour and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (14.5 mg).

[0142] Example 9x *N*-(Cyclopropylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-

b][1,3]thiazole-7-amine hydrochloride

To a mixture of *N*-(cyclopropylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (8.38 mg) and ethyl acetate (0.5 mL) was added hydrochloric acid in diethyl ether (1M, 17.2 μL). The mixture was stirred at room temperature for 1.5 hours and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (9.22 mg).

[0143] Example 10x 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine hydrochloride

To a mixture of 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (6.98 mg) and ethyl acetate (0.5 mL) was added hydrochloric acid in diethyl ether (1M, 14.7 μL). The mixture was stirred at room temperature for 1.5 hours and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (7.84 mg).

[0144] Example 11x *N*-(Cyclopropylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine phosphate

To a mixture of *N*-(cyclopropylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (30.0 mg) and ethyl acetate (0.6 mL) was added phosphoric acid (14.6M, 4.00 μL). The mixture was stirred at room temperature for 5 minutes and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (35.8 mg).

[0145] Example 12x 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-[(2-methylcyclopropyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine methanesulfonate

To a mixture of 3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-[(2-methylcyclopropyl)methyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (14.6 mg) and ethyl acetate (0.5 mL) was added methanesulfonic acid (1.90 μL). The mixture was stirred at room temperature for 1 hour and the solvent was removed by blowing nitrogen stream and dried to obtain

the title compound (17.4 mg).

[0146] Example 13x 3-[2-Chloro-6-methoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine methanesulfonate

To a mixture of 3-[2-chloro-6-methoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (10.7 mg) and ethyl acetate (0.5 mL) was added methanesulfonic acid (1.45 μL). The mixture was stirred at room temperature for 1 hour and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (12.8 mg).

[0147] Example 14x 4-{7-[(Cyclopropylmethyl)(tetrahydrofuran-3-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile hydrobromide

To a mixture of 4-{7-[(cyclopropylmethyl)(tetrahydrofuran-3-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile (8.0 mg) and methanol (1 mL) was added hydrobromic acid (8.84M, 2.4 μL), and the mixture was stirred at room temperature for 1 hour and the solvent was distilled off under reduced pressure. Methanol (1 mL) was added to the residue and the solvent was distilled off under reduced pressure. Ethyl acetate (1 mL) was added to the resultant residue and the solvent was distilled off under reduced pressure and dried to obtain the titled compound (8.0 mg).

[0148] Example 15x 4-{7-[(Cyclopropylmethyl)(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile hydrochloride

To a mixture of 4-{7-[(cyclopropylmethyl)(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile (26.4 mg) and ethyl acetate (0.5 mL) was added hydrochloric acid in diethyl ether (1M, 54.7 μL). The mixture was stirred at room temperature for 1 hour and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (28.4 mg).

[0149] Example 16x *N*-(Cyclopropylmethyl)-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-3-(2,4,6-trimethoxyphenyl)-pyrazolo[5,1-*b*][1,3]thiazole-7-amine hydrochloride

To a mixture of *N*-(Cyclopropylmethyl)-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-3-(2,4,6-trimethoxyphenyl)-pyrazolo[5,1-*b*][1,3]thiazole-7-amine (6.51 mg) and ethyl acetate (0.5 mL) was added hydrochloric acid in diethyl ether (1M, 13.4 μL). The mixture was stirred at room temperature for 1.5 hours and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (7.41 mg).

[0150] Example 17x 3-{4-[(Cyclobutyloxy)methyl]-2,6-dimethoxyphenyl}-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine phosphate

To a mixture of 3-{4-[(cyclobutyloxy)methyl]-2,6-dimethoxyphenyl}-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine (30.0 mg) and ethyl acetate (0.6 mL) was added phosphoric acid (14.6M, 4.00 μL). The mixture was stirred at room temperature for 5 minutes and the solvent was removed by blowing nitrogen stream and dried to obtain the title compound (36.1 mg).

[0151] [Pharmacological Test Example]

The binding capacities of the compounds of the invention for CRF1 receptor (CRFR1) were evaluated. The test methods and results were as described below.

[0152] Test Example 1

<CRFR1 binding test>

(1) Preparation of CRFR1-expressing cells

The membrane fraction of human CRFR1 high-expressing cells was used as the material for a CRFR1 binding experiment. The CRFR1-expressing cells were prepared in the following manner. The full-length CRFR1 gene was obtained by PCR using human brain cDNA library (QuickClone™ Clontech). The obtained DNA fragment was inserted into a cloning vector and the nucleotide sequence was confirmed. cDNA having the proper nucleotide sequence was linked to an expression vector (pcDNA3.1™, Invitrogen). The CRFR1 expression vector was introduced into HEK293 cell, and the resistant cells which proliferated in culture medium containing G418 (1 mg/ml) were cloned by the limiting dilution method. Out of the cloned cells, cells having high binding affinity between the membrane fraction per unit of protein and sauvagine were selected according to the following

binding experiment. And the selected cells were used for the experiments.

[0153] (2) Preparation of membrane fraction

The cloned cells obtained in (1) were collected and suspended in ice-cooled membrane buffer (50 mM Tris-HCl, 5 mM $MgCl_2$, 2 mM EGTA, 1 mM DTT, protease inhibitor cocktail (COMPLETE™, Roche Diagnostics) pH 7.3), and then the cells were disrupted with a Polytron (KINEMATICA) while cooling on ice (level 5, 10 seconds, 2-5 times, ice-cooling) and then centrifuged (2,000 rpm, 5 minutes, 4°C), after which the supernatant was collected. Membrane buffer was added to the precipitate, and the mixture was subjected to Polytron treatment (same conditions as above) and centrifuged (same conditions as above), and the obtained supernatant was collected and combined with the previous supernatant. This was centrifuged (13,000 rpm (18,000 × g), 30 minutes, 4°C) to prepare cell membranes. The precipitated cell membranes were suspended in membrane buffer and disrupted with a Polytron (level 5, 10 seconds, 3-5 times, ice-cooling) to prepare a dispersed suspension. The protein assay was performed.

The following method (1) or (2) was performed for use as the cell membrane fraction.

(1) The above dispersed suspension was diluted with membrane buffer containing 0.1% BSA to a protein concentration of 200 μg/ml, for use as the cell membrane fraction.

(2) The above dispersed suspension was frozen for preservation, and if needed, thawed, re-dispersed and diluted for used as the cell membrane fraction.

[0154] (3) Binding experiment:

A binding competition experiment with CRF was conducted by the SPA (GE Healthcare) method using a 96-well plate. A mixture of 5 μg of the cell membrane fraction protein, 1 mg of SPA beads and 100 pM ^{125}I-CRF (Perkin Elmer) was allowed to stand at room temperature for at least 2 hours in the presence of a test compound, and the radioactivity of each well after centrifugation (1,200 rpm (260 × g), 5 minutes, room temperature) was measured with a TopCount (registered trademark; Perkin Elmer).

[0155] (4) Calculation of binding capacity

The radioactivity with addition of a 4,000-fold excess of non-radioactive sauvagine as the nonspecific binding was subtracted from each value, and the

resulting value was expressed as a percentage (% of control), with 100% as the radioactivity without addition of the test compound (control). The IC_{50} value was calculated from a binding inhibition curve drawn with test compound concentration on the horizontal axis and % (% of control) on the vertical axis.

[0156] <Test results>

As shown by the following table, the compounds of the invention exhibit excellent binding capacity for CRFR1.

[0157] [Table 1]

Compound No. (Example No.)	CRF1 receptor binding capacity IC_{50} (nM)
1	52
2	70
3	65
4	34
5	29
6	39
7	46
8	63
9	101
10	98
11	37
12	82
13	63
14	90
15	70
16	29
17	36

[0158] Test Example 2

Evaluation of anxiolytic effect by mice in light/dark box test in mice

(1) Test procedure:

The light/dark box test in mice was carried out according to a modified method of Belzung C., Misslin R., Vogel E. et al. (Reference; Behavioural effects of the benzodiazepine receptor partial agonist RO16-6028 in mice, Psychopharmacology, 97, 388-391, 1989). The test apparatus used was a light/dark box comprising a covered black acrylic box (dark box; 15 x 10 x 20 cm), an uncovered white acrylic box (light box; 15 x 20 x 20 cm) and a black acrylic tunnel (10 x 7 x 4.5 cm) which connects dark box and light box and enables a mouse to freely move back and forth between the dark box and light box. In this test

apparatus, however, a transparent acrylic polymer was used for the front side (20 x 20 cm) and back side (20 x 20 cm) of the light box to allow observation of the behavior. After setting illumination so that the light intensity of the floor of the light box was 150 Lux, 5-week-old male Balb/c mice (purchased from Nihon Charles River) were introduced into the dark box at the beginning of the test. For the test, the tested compound was suspended in 5% dimethylsulfoxide, 5% Cremopor EL and 90% physiological saline and orally administered to the test animals one hour prior to the start of the test.

[0159] (2) Calculation of anxiolytic effect:

The behavior of the mice was observed for 5 minutes after start of the test. The time spent in the light box was measured as an index of the anxiolytic effect, with "spend in the light box" defined as the state in which all limbs of the mice were on the floor of the light box. The minimum dose which significantly prolonged the time spent in the light box in comparison with that of vehicle-treated group was determined as the minimum effective dose (MED). The statistical significance between the vehicle-treated group and the test compound-treated groups was analyzed by one way analysis of variance followed by Dunnett multiple comparison when multiple doses were set for the same test, and by the Mann-Whitney U test when only one dose was set.

[0160] <Test results>

The compounds of Examples 1, 2, 3, 4, 5, 9, 10, 13 and 14 exhibited an excellent anxiolytic effects in the light/dark box test in mice, with statistically significant effects being observed at 30 mg/kg (oral administration).

[0161] [Table 2]

Compound No. (Example No.)	Effective Dose (mg/kg)
1	30
2	30
3	30
4	30
5	30
9	30
10	30
13	30
14	30

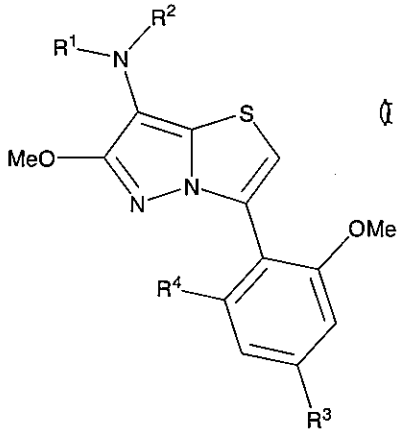
Industrial Applicability

[0162] According to the invention it is possible to provide pharmaceutical compositions comprising 3-phenylpyrazolo[5,1-*b*]thiazole compounds or salts thereof, which exhibit CRF receptor antagonism. The compounds or salts thereof according to the invention have excellent CRF receptor antagonism, and sufficient pharmacological activity, safety and pharmacokinetic properties as drugs.

[0163] The pharmaceutical compositions of the invention are useful for treatment or prevention of diseases associated with CRF and/or CRF receptors, and are particularly useful as therapeutic or prophylactic agents for depression, depressive symptoms, anxiety, irritable bowel syndrome, sleep disorder, insomnia, alcohol dependence, alcohol withdrawal symptoms, drug dependence, drug withdrawal symptoms, stress-related gastrointestinal dysfunction, anorexia nervosa, eating disorder, postoperative ileus, ischemic neuropathy, apoplexy, excitotoxic neuropathy, convulsion, epilepsy, hypertension, schizophrenia, bipolar disorder or dementia.

CLAIMS

1. A compound represented by the following formula (I) or salt thereof.



wherein

R^1 represents the formula $-A^{11}-A^{12}$;

R^2 represents tetrahydrofurylmethyl, tetrahydropyranylmethyl or tetrahydropyranyl;

A^{11} represents a single bond, methylene or 1,2-ethylene;

A^{12} represents C1-6 alkyl or C3-6 cycloalkyl, or C3-6 cycloalkyl having methyl;

R^3 represents methoxy, cyano, cyclobutyloxymethyl, methoxymethyl or ethoxymethyl; and

R^4 represents methoxy or chlorine.

2. A compound or salt thereof as claimed in claim 1, wherein R^2 is tetrahydropyran-4-yl, tetrahydropyran-3-yl, (tetrahydropyran-4-yl)methyl or (tetrahydrofuran-3-yl)methyl.

3. A compound or salt thereof as claimed in claim 1 or 2, wherein R^1 is n-propyl, n-butyl, n-pentyl, cyclopropylmethyl, cyclobutylmethyl, 2-(cyclopropyl)ethyl or (2-methylcyclopropyl)methyl.

4. *N*-Butyl-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

5. *N*-Butyl-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

6. *N*-(2-Cyclopropylethyl)-3-[4-(ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

7. 3-[4-(Ethoxymethyl)-2,6-dimethoxyphenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-3-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

8. *N*-(Cyclobutylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

9. *N*-(Cyclopropylmethyl)-3-[2,6-dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

10. 3-[2,6-Dimethoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

11. 3-[2-Chloro-6-methoxy-4-(methoxymethyl)phenyl]-6-methoxy-*N*-propyl-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

12. 4-{7-[(Cyclopropylmethyl)(tetrahydrofuran-3-ylmethyl)amino]-6-methoxypyrazolo[5,1-*b*][1,3]thiazol-3-yl}-3,5-dimethoxybenzonitrile or salt thereof.

13. *N*-(Cyclopropylmethyl)-6-methoxy-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-3-(2,4,6-trimethoxyphenyl)-pyrazolo[5,1-*b*][1,3]thiazole-7-amine or salt thereof.

14. A pharmaceutical composition comprising a compound or salt thereof according to any one of claims 1 to 13 as an active ingredient.

15. A compound or salt thereof according to any one of claims 1 to 13 for use in the treatment of depression, depressive symptoms, anxiety, irritable bowel syndrome, sleep disorder, insomnia, alcohol dependence, alcohol withdrawal symptoms, drug dependence, drug withdrawal symptoms, stress-related gastrointestinal dysfunction, anorexia nervosa, eating disorder, postoperative ileus, ischemic neuropathy, apoplexy, excitotoxic neuropathy, convulsion, epilepsy, hypertension, schizophrenia, bipolar disorder or dementia.

16. A compound or salt thereof according to any one of claims 1 to 13 for use in the treatment of depression, depressive symptoms, anxiety or irritable bowel syndrome.