PYRAZOLOTHIAZOLE COMPOUND AND MEDICINE COMPRISING SAME

Field of the Invention

[0001]

The present invention relates to a pharmaceutical composition comprising a novel pyrazolothiazole compound, or a pharmaceutically acceptable salt thereof, or a solvate thereof as an active ingredient.

Background Art

[0002]

Tyrosine kinases are a group of enzymes that specifically phosphorylate a tyrosine residue in proteins. The enzymes have a significant role in the intracellular signal transduction pathways and relate to a wide variety of biological functions including cell survival, differentiation, proliferation, and secretion. Janus Kinase (also referred to as JAK) family is known as that of intracellular tyrosine kinases involving a cytokine signaling. JAK family includes the four types of enzymes: JAK1, JAK2, JAK3 and Tyrosine Kinase 2 (also referred to as Tyk2). Once a cytokine associates with its respective cytokine receptor, JAK is phosphorylated, and a tyrosine residue of the receptor is then phosphorylated. Then, signal transducer and activator of transcription (also referred to as "STAT"), which exists in cells, will become

associated with the phosphorylated tyrosine residue of the receptor, and a tyrosine residue of STAT is phosphorylated by JAK. The phosphorylated STATs form a dimer, and the dimer translocates into the nucleus and activates transcription of target gene, which leads to activation of the cells. JAK/STAT pathways are the key intracellular signal transduction pathways of cytokines in immunocompetent cells (Non-Patent Literature 1). About 40 types of cytokine signal transductions are mediated by a combination of the four JAKs and seven STATs, and abnormalities of a cytokine production and a cytokine signaling are believed to have an intimate involvement in not only various immune and inflammatory diseases, such as autoimmune diseases and allergic diseases, but also diseases having diverse pathologies such as cancers. Compounds suppressing the activation of these JAK/STAT pathways draw attention as new therapeutics for these diseases, and, in fact, JAK inhibitors have already been approved in United States and Japan as a therapeutic for myelofibrosis, polycythemia vera and rheumatoid arthritis. Further, effects of such compounds are expected in the treatment of other autoimmune diseases (such as psoriatic arthritis, juvenile arthritis, Castleman's disease, systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, inflammatory bowel disease, Behçet's disease,

myasthenia gravis, type 1 diabetes mellitus, immunoglobulin nephropathy, autoimmune thyroid diseases, psoriasis, scleroderma, lupus nephritis, dry eye, vasculitis (such as Takayasu's arteritis, giant cell arteritis, microscopic polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis), dermatomyositis, polymyositis and neuromyelitis optica), inflammatory diseases (such as atopic dermatitis, contact dermatitis, eczema, pruritus, food allergies, bronchial asthma, eosinophilic pneumonia, chronic obstructive pulmonary disease, allergic rhinitis, chronic sinusitis, eosinophilic sinusitis, nasal polyp, allergic conjunctivitis, osteoarthritis, ankylosing spondylitis, Kawasaki disease, Buerger's disease, polyarteritis nodosa and IgA vasculitis), proliferative diseases (such as solid cancers, blood cancers, lymph malignant tumor, myeloproliferative diseases, multiple myeloma, pulmonary fibrosis and eosinophilia), sudden hearing loss, diabetic nephropathy, alopecia areata, bone marrow transplant rejection or organ transplant rejection. Currently, the clinical trials are in progress for some diseases as listed above in Japan, United States and Europe.

[0003]

Specifically, various biological studies have demonstrated an important role of JAK1 in the signal

transductions of many cytokines (See Non-Patent Literatures 2, 3 and 4), indicating that JAK1 inhibitors are useful in the treatment of the diseases, such as autoimmune diseases: psoriatic arthritis (See Non-Patent Literature 5), juvenile arthritis (See Non-Patent Literature 6), Castleman's disease (See Non-Patent Literature 6), systemic lupus erythematosus (See Non-Patent Literature 7), Sjögren's syndrome (See Non-Patent Literature 8), multiple sclerosis (See Non-Patent Literature 9), inflammatory bowel disease (See Non-Patent Literature 10), Behçet's disease (See Non-Patent Literature 11), myasthenia gravis (See Non-Patent Literature 12), type 1 diabetes mellitus (See Non-Patent Literature 9), immunoglobulin nephropathy (See Non-Patent Literature 13), autoimmune thyroid diseases (See Non-Patent Literature 14), psoriasis (See Non-Patent Literature 15), scleroderma (See Non-Patent Literature 16), lupus nephritis (See Non-Patent Literature 17), dry eye (See Non-Patent Literature 18), vasculitis (See Non-Patent Literatures 19, 20, 21, 22 and 23), dermatomyositis (See Non-Patent Literature 24), polymyositis (See Non-Patent Literature 24), neuromyelitis optica (See Non-Patent Literature 25), inflammatory diseases: atopic dermatitis (See Non-Patent Literature 26), contact dermatitis (See Non-Patent Literature 27), eczema (See Non-Patent Literature 28), pruritus (See Non-Patent Literature 29), food allergies

(See Non-Patent Literature 30), bronchial asthma (See Non-Patent Literature 31), eosinophilic pneumonia (See Non-Patent Literature 32), chronic obstructive pulmonary disease (See Non-Patent Literature 33), allergic rhinitis (See Non-Patent Literature 31), chronic sinusitis (See Non-Patent Literature 34), eosinophilic sinusitis, nasal polyp (See Non-Patent Literature 35), allergic conjunctivitis (See Non-Patent Literature 36), osteoarthritis (See Non-Patent Literature 37), ankylosing spondylitis (See Non-Patent Literature 6), Kawasaki disease (See Non-Patent Literature 38), Buerger's disease (See Non-Patent Literature 39), polyarteritis nodosa (See Non-Patent Literature 40), IgA vasculitis (See Non-Patent Literature 41), proliferative diseases: solid cancers, blood cancers, lymph malignant tumor, myeloproliferative diseases, multiple myeloma (See Non-Patent Literatures 42, 43 and 44), sudden hearing loss (See Non-Patent Literature 45), diabetic nephropathy (See Non-Patent Literature 46), alopecia areata (See Non-Patent Literature 47), bone marrow transplant rejection or organ transplant rejection, etc. For example, the following clinical trials are in progress. Rheumatoid arthritis (https://clinicaltrials.gov/ NCT01888874 and NCT02049138), Crohn's disease (https://clinicaltrials.gov/ NCT02365649), non small cell lung cancer (https://clinicaltrials.gov/ NCT02257619),

pancreatic cancer (https://clinicaltrials.gov/ NCT01858883), myelofibrosis (https://clinicaltrials.gov/ NCT01633372) and psoriasis (https://clinicaltrials.gov/ NCT02201524).

[0004]

Further, among the cytokine signalings associated with JAK1, the inhibitors for the following cytokines have already been launched.

(1) IL-6 (also referred to as interleukin-6): therapeutic agents for rheumatoid arthritis, juvenile arthritis and Castleman's disease (See Non-Patent Literatures 48, 49 and 50).

(2) IL-2: therapeutic agent for acute rejection following renal transplantation (See Non-Patent Literature 51).

[0005]

In addition, the clinical trials on the following cytokine inhibitors are in progress.

(3) IL-4 and IL-13: therapeutic agent for bronchial asthma, atopic dermatitis, eosinophilic sinusitis, nasal polyp and eosinophilic esophagitis (See Non-Patent Literature 31).

(4) IL-13: therapeutic agent for pulmonary fibrosis (See https://clinicaltrials.gov/ NCT02036580).

(5) IL-5: therapeutic agent for bronchial asthma, chronic obstructive pulmonary disease, eosinophilia, eosinophilic granulomatosis with polyangiitis, eosinophilic esophagitis, eosinophilic sinusitis/nasal polyp and atopic dermatitis

(See Non-Patent Literature 31 and Non-Patent Literature 52).

(6) IFNα (also referred to as interferon-α): therapeutic agent for systemic lupus erythematosus (See Non-Patent Literature 7).

(7) IL-31: therapeutic agent for atopic dermatitis (https://clinicaltrials.gov/ NCT01986933).

(8) TSLP (also referred to as thymic stromal lymphopoietin): therapeutic agents for bronchial asthma (https://clinicaltrials.gov/ NCT02054130) and atopic dermatitis (https://clinicaltrials.gov/ NCT00757042).

[0006]

Thus, the inhibition of JAK1 signal is a preferred means for the prevention or treatment of the diseases caused by an abnormality of JAK1, such as autoimmune diseases, inflammatory diseases and proliferative diseases.

[0007]

As a JAK1 inhibitor, [1,2,4]triazolo[1,5-a]pyridines (See Patent Literatures 1 and 2), tricyclic pyrazinones (See Patent Literature 3), pyrrolopyrimidines (See Patent Literatures 4 to 7), phthalazines (See Patent Literature 8), imidazopyrrolopyridines (See Patent Literature 9 and Non-Patent Literature 53), diamino-1,2,4-triazoles (See Non-Patent Literature 54), pyrazolo[1,5-a]pyridines (See Patent Literature 10), imidazo[1,2-a]pyridines (See Patent Literatures 11 and 12), benzimidazoles (See Patent

Literature 13), 7-azaindoles (See Patent Literature 14) are reported. However, none of the documents as mentioned disclose pyrazolo[5,1-b][1,3]thiazole compounds.

Prior Art Documents

Non-Patent Literatures

[0008]

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[Non-Patent Literature 24] Gono et al., Rheumatology, 2014, 53, 2196-2203.

[Non-Patent Literature 25] Araki et al., Neurology, 2014, 82, 1302-1306.

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[Non-Patent Literature 52] Kouro et al., Int. Immunol., 2009, 21, 1303-1309.

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Patent Literature

[0009]

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[Patent Literature 2] WO 2010/010190

[Patent Literature 3] WO 2012/085176

[Patent Literature 4] WO 2009/114512

[Patent Literature 5] WO 2011/075334

[Patent Literature 6] WO 2012/022045

[Patent Literature 7] WO 2012/054364

[Patent Literature 8] WO 2012/037132

[Patent Literature 9] WO 2011/086053

[Patent Literature 10] WO 2011/101161

[Patent Literature 11] WO 2011/076419

[Patent Literature 12] JP 2011/136925

[Patent Literature 13] WO 2005/066156

[Patent Literature 14] WO 2007/084557

Summary of the Invention

Problem to be solved by the invention

[0010]

An object of the present invention is to provide a compound with an excellent JAK1 inhibitory activity.

Means for solving the problem

[0011]

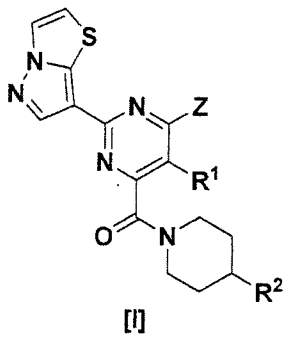
The present invention is based on the inventor's discovery that a compound represented by the following general formula [I] or a pharmaceutically acceptable salt thereof, or a solvate thereof (herein after referred to as "the compound of the invention") has an excellent JAK1 inhibitory activity.

[0012]

Thus, the present inventions as in the following (I) to (XVII) are disclosed.

(I) A pyrazolothiazole compound represented by the formula [I]:

[Formula 1]



[I]

wherein,

R^1 is hydrogen, alkyl or alkoxy;

Z is $-OR^3$ or $-NR^4R^5$;

in which

R^3 is alkyl, alkyl substituted with cycloalkyl, cycloalkyl, aryl or heteroaryl,

R^4 is hydrogen or alkyl;

R^5 is alkyl, cycloalkyl or saturated heterocyclic group, said alkyl and cycloalkyl in R^5 is optionally substituted with one or two groups selected from the group consisting of the following (1) to (6):

(1) hydroxy,

(2) alkoxy, and difluoroalkoxy,

(3) cycloalkyl, cycloalkyl substituted with (difluoroalkoxy)alkyl, and cycloalkyl substituted with alkoxyalkyl,

(4) saturated heterocyclic group optionally substituted with (difluoroalkoxy)alkyl,

(5) aryl, aryl substituted with halogen, and aryl substituted with alkoxy, and

(6) nitrile, and

said saturated heterocyclic group in R^5 is optionally substituted with one or two groups selected from the following (1) to (3):

(1) alkyl,

(2) alkylcarbonyl, and

(3) alkoxycarbonyl;

R^2 is hydroxy or $-NHR^8$,

in which

R^8 is heteroaryl, heteroaryl substituted with halogen, heteroaryl substituted with alkyl, $-COL^1$, $-COOL^2$ or $-SO_2L^3$,

said L^1 is a group selected from the group consisting of the following (1) to (5):

(1) alkyl, monohaloalkyl, dihaloalkyl, trihaloalkyl, and alkyl substituted with alkoxy

(2) cycloalkyl,

(3) aryl,

(4) heteroaryl, and

(5) dialkylamino, and cycloalkylamino,

said L^2 is a group selected from the group consisting of the following (1) to (3):

(1) alkyl, monohaloalkyl, dihaloalkyl, trihaloalkyl, and alkyl substituted with alkoxy,

(2) cycloalkyl, and

(3) dialkylaminoalkyl, and

said L^3 is alkyl or cycloalkyl,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[0013]

(II) The pyrazolothiazole compound as described in (I) or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein R^1 is hydrogen.

[0014]

(III) The pyrazolothiazole compound as described in (II) or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein

Z is $-NR^4R^5$;

in which

R^4 is hydrogen,

R^5 is alkyl or cycloalkyl,

said alkyl and cycloalkyl in R^5 are optionally substituted with a group selected from the group consisting of the following (1) to (3):

(1) hydroxy,

(2) alkoxy, and

(3) cycloalkyl,

R^2 is hydroxy or $-NHR^8$,

R^8 is heteroaryl, heteroaryl substituted with halogen, heteroaryl substituted with alkyl, $-COL^1$ or $-COOL^2$,

said L^1 is a group selected from the group consisting of the following (1) to (4):

(1) alkyl, monohaloalkyl, dihaloalkyl, trihaloalkyl, and alkyl substituted with alkoxy,

(2) cycloalkyl,

(3) aryl, and

(4) heteroaryl, and

said L^2 is alkyl, monohaloalkyl, dihaloalkyl, trihaloalkyl, alkyl substituted with alkoxy or cycloalkyl.

[0015]

(IV) The pyrazolothiazole compound as described in (III) or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein

R^5 is alkyl, alkyl substituted with hydroxy, alkyl substituted with cyclopropyl or alkyl substituted with alkoxy, and

R^2 is $-NHR^8$.

[0016]

(V) The pyrazolothiazole compound as described in (III) or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein

R^5 is alkyl having 2 to 6 carbon atoms or alkyl substituted with cyclopropyl,

R^2 is $-NHR^8$,

R^8 is $-COL^1$ or $-COOL^2$,

said L^1 is alkyl having 2 to 6 carbon atoms or cyclopropyl, and

said L^2 is alkyl or cyclopropyl.

[0017]

(VI) The pyrazolothiazole compound as described in (I) which is any one of the following (1) to (135):

(1) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(2) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(3) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(4) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)acetamide,

(5) N-(1-{[6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(6) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(7) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(8) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclopropyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(9) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclobutyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(10) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclopentyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(11) N-[1-({6-[({4-[(difluoromethoxy)methyl]tetrahydro-2H-pyran-4-yl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-

yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(12) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(13) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(14) N-(1-{[6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(15) N-[1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(16) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(17) N-(1-{[6-{[(2S)-1-(difluoromethoxy)propan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(18) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2,2-difluoroacetamide,

(19) N-(1-{[6-{[(1S,2S)-2-methoxycyclopentyl]amino}-2-

(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(20) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(21) 1-fluoro-2-methylpropan-2-yl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(22) methyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(23) [6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(24) methyl (1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(25) methyl (1-{[6-{[(2S)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(26) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(27) ethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)carbamate,

(28) propan-2-yl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(29) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide,

(30) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)pyridine-3-carboxamide,

(31) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)thiophene-2-carboxamide,

(32) N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(33) 1-cyclopropyl-3-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)urea,

(34) [6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyrimidin-2-ylamino)piperidin-1-yl]methanone,

(35) N-(1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(36) N-[1-({6-[(1-methylcyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(37) N-[1-({6-[(1-methoxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(38) methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(39) ethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(40) propan-2-yl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(41) N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide,

(42) N-(1-{[6-(cyclopropylmethoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(43) N-[1-({6-[(3,3-dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(44) N-(1-{[6-(cyclobutyloxy)-2-(pyrazolo[5,1-

b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(45) N-(1-{[6-(cyclopentyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(46) N-(1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(47) N-[1-({6-[(1-hydroxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(48) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,2-oxazol-3-ylamino)piperidin-1-yl]methanone,

(49) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone,

(50) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-methyl-1,2-oxazol-5-yl)amino]piperidin-1-yl}methanone,

(51) N-(1-{[6-{[(2S)-1-hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(52) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(53) methyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(54) propan-2-yl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(55) methyl [1-({6-[(1-hydroxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(56) [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(57) methyl (1-{[6-{[(2S)-1-hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(58) methyl [1-({6-[(3,3-dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(59) methyl (1-{[6-(cyclobutyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(60) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)methanesulfonamide,

(61) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-

(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanesulfonamide,

(62) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)ethanesulfonamide,

(63) N-(1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methylpropanamide,

(64) N-(1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2,2-difluoroacetamide,

(65) ethyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(66) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyridin-2-ylamino)piperidin-1-yl]methanone,

(67) ethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(68) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone,

(69) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyrimidin-2-ylamino)piperidin-1-

yl]methanone,

(70) methyl [1-({6-[(2-methylbutan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(71) (4-hydroxypiperidin-1-yl)[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone,

(72) propyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(73) propyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(74) propyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(75) propyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(76) propyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(77) methyl [1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(78) 2-methoxyethyl (1-{[6-{[(1R)-1-

cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(79) 2-methoxyethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(80) 2-methoxyethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(81) 2-methoxyethyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(82) N-(1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide,

(83) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide,

(84) methyl [1-({6-[{[1-(methoxymethyl)cyclopropyl]methyl}(methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(85) 2,2-difluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(86) 2,2-difluoroethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-

yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(87) 2,2-difluoroethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(88) 2,2-difluoroethyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(89) tert-butyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(90) 2-methoxyethyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(91) 2-(dimethylamino)ethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(92) 2,2,2-trifluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(93) 2,2,2-trifluoroethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(94) 2-methoxy-N-(1-{[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-

yl)acetamide,

(95) N-(1-{[6-(2-ethylbutoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(96) methyl (1-{[6-(pentan-3-yloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(97) methyl (1-{[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(98) N-[1-({6-[(2-ethylbutyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(99) N-(1-{[6-(pentan-3-yloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(100) methyl [1-({6-[methyl(pentan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(101) methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(102) N-(1-{[6-(2-ethylbutoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide,

(103) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide,

(104) N-[1-({6-[methyl(pentan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(105) [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone,

(106) N-[1-({6-[(2-methoxy-2-methylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(107) (4-hydroxypiperidin-1-yl){6-[methyl(pentan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}methanone,

(108) N-(1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide,

(109) N-(1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(110) N-(1-{[6-{[(2S)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(111) N-(1-{[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-

b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(112) methyl [1-({6-[(2S)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(113) methyl [1-({6-[(2R)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(114) N-[1-({6-[(1-methylcyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(115) [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(5-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone,

(116) 2-methyl-N-[1-({6-[(2-methylbutan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(117) N-[1-({6-[(2S)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(118) methyl [1-({6-[tert-butyl(methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(119) cyclopropyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)carbamate,

(120) cyclopropyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(121) 2,2-difluoro-N-(1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(122) 3-[1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]-1,1-dimethylurea,

(123) 3-(1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-1,1-dimethylurea,

(124) propan-2-yl [1-({6-[(3-methyloxetan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(125) methyl [1-({6-[(dicyclopropylmethyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(126) methyl (1-{[6-phenoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(127) tert-butyl 4-{[6-({4-[(methoxycarbonyl)amino]piperidin-1-yl}carbonyl)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]amino}piperidine-1-carboxylate,

(128) methyl (1-{[6-(piperidin-4-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(129) methyl [1-({6-[(1-cyanocyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(130) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(131) methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(132) methyl [1-({6-[(2S)-butan-2-ylamino]-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(133) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(134) methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(135) methyl (1-{[2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-(pyridin-3-yloxy)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

or a pharmaceutically acceptable salt thereof, or a solvate

thereof.

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(VII) The pyrazolothiazole compound described in (I) which is any one of the following (1) to (58):

(1) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(2) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(3) N-(1-{[6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(4) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(5) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclopropyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(6) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclobutyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(7) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclopentyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(8) N-[1-({6-[({4-[(difluoromethoxy)methyl]tetrahydro-2H-pyran-4-yl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(9) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(10) N-(1-{[6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(11) N-[1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(12) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(13) N-(1-{[6-{[(2S)-1-(difluoromethoxy)propan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(14) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(15) ethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(16) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide,

(17) N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(18) propan-2-yl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(19) N-(1-{[6-(cyclopropylmethoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(20) N-[1-({6-[(3,3-dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(21) N-(1-{[6-(cyclobutyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(22) N-[1-({6-[(1-hydroxy-2-methylpropan-2-yl)amino]-2-

(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(23) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone,

(24) N-(1-{[6-{[(2S)-1-hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(25) methyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(26) propan-2-yl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(27) methyl [1-({6-[(1-hydroxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(28) [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(29) methyl (1-{[6-{[(2S)-1-hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(30) methyl [1-({6-[(3,3-dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl}carbonyl)piperidin-4-yl]carbamate,

(31) methyl (1-{[6-(cyclobutyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(32) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanesulfonamide,

(33) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)ethanesulfonamide,

(34) ethyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(35) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyridin-2-ylamino)piperidin-1-yl]methanone,

(36) propyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(37) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide,

(38) 2,2-difluoroethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(39) 2,2-difluoroethyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(40) tert-butyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(41) 2-methoxyethyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(42) 2-(dimethylamino)ethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(43) 2,2,2-trifluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(44) 2,2,2-trifluoroethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(45) methyl (1-{[6-(pentan-3-yloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(46) N-[1-({6-[(2-ethylbutyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(47) N-(1-{[6-(pentan-3-yloxy)-2-(pyrazolo[5,1-

b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(48) methyl [1-({6-[(2S)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(49) methyl [1-({6-[(2R)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(50) N-[1-({6-[(1-methylcyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(51) methyl [1-({6-[tert-butyl(methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(52) cyclopropyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(53) propan-2-yl [1-({6-[(3-methyloxetan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(54) methyl [1-({6-[(1-cyanocyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(55) methyl [1-({6-[(2S)-butan-2-ylamino]-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl}carbonyl)piperidin-4-yl]carbamate,

(56) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(57) methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate, and

(58) methyl (1-{[2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-(pyridin-3-yloxy)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[0019]

(VIII) The pyrazolothiazole compound described in (I) which is any one of the following (1) to (8):

(1) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(2) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(3) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(4) ethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(5) N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(6) propan-2-yl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(7) methyl [1-({6-[(2S)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate, and

(8) methyl [1-({6-[(2R)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[0020]

(IX) A pharmaceutical composition comprising the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of (I) to (VIII) as an active ingredient.

[0021]

(X) A JAK1 inhibitor comprising the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of (I) to (VIII) as an active ingredient.

[0022]

(XI) A therapeutic agent for an inflammatory disease comprising the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of (I) to (VIII) as an active ingredient.

[0023]

(XII)

The therapeutic agent according to (XI) wherein the inflammatory disease is atopic dermatitis, eczema, bronchial asthma, eosinophilic pneumonia, chronic obstructive pulmonary disease, allergic rhinitis, eosinophilic sinusitis, nasal polyp, ankylosing spondylitis or eosinophilic esophagitis.

[0024]

(XIII)

A therapeutic agent for an autoimmune disease comprising the pyrazolothiazole compound or a

pharmaceutically acceptable salt thereof or a solvate thereof according to any one of (I) to (VIII) as an active ingredient.

[0025]

(XIV) The therapeutic agent according to (XIII) wherein the autoimmune disease is rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, Castleman's disease, systemic lupus erythematosus, Sjögren's syndrome, inflammatory bowel disease, psoriasis, scleroderma, dry eye, Takayasu's arteritis, giant cell arteritis, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis or neuromyelitis optica.

[0026]

(XV) A therapeutic agent for a proliferative disease comprising the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of (I) to (VIII) as an active ingredient.

[0027]

(XVI) The therapeutic agent according to (XV) wherein the proliferative disease is solid cancers, blood cancers,

lymph malignant tumor, myeloproliferative diseases, multiple myeloma, pulmonary fibrosis or eosinophilia.

[0028]

(XVII) A therapeutic agent for diabetic nephropathy, alopecia areata, bone marrow transplant rejection or organ transplant rejection comprising the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of (I) to (VIII) as an active ingredient.

[0029]

The terms as used herein are defined below.

The term "halogen" includes fluorine, chlorine, bromine or iodine atom. Specially, fluorine atom is preferrable.

[0030]

The term "alkyl" includes, for example, an alkyl of straight or branched chain having 1 to 10 carbon atoms, preferably 1 to 8 carbon atoms, more preferably 1 to 6 carbon atoms. Specifically, the term may include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, sec-pentyl, 1-ethylpropyl, 1,2-dimethylpropyl, tert-pentyl, 2-methylbutyl, isopentyl,

neopentyl, n-hexyl, sec-hexyl, 1-ethylbutyl, isohexyl, neohexyl, 1,1-dimethylbutyl, thexyl, 2-ethylbutyl, 1,2,2-trimethylpropyl, 2,2-dimethylbutyl, heptyl, isoheptyl, octyl and isooctyl.

[0031]

Examples of the alkyl moiety in "(difluoroalkoxy)alkyl", "alkoxyalkyl", "dialkylamino", "dialkylaminoalkyl", "alkylcarbonyl", "monohaloalkyl", "dihaloalkyl", "trihaloalkyl" may include the same as described above for "alkyl".

[0032]

The term "monohaloalkyl" refers to a group wherein an "alkyl" as defined above is substituted with a "halogen" as defined above. Specifically, the term may include, for example, monofluoromethyl, monochloromethyl and monofluoroethyl.

[0033]

The term "dihaloalkyl" refers to a group wherein an "alkyl" as defined above is substituted with two "halogens" as defined above. Specifically, the term may include, for example, difluoromethyl, difluoroethyl and 1,2-difluoropropyl.

[0034]

The term "trihaloalkyl" refers to a group wherein an "alkyl" as defined above is substituted with three "halogens" as defined above. Specifically, the term may include, for example, trifluoromethyl, trichloromethyl and trifluoroethyl.

[0035]

The term "alkoxy" may include, for example, a straight or branched chain alkoxy having 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms. Specifically, the term may include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentyloxy, n-hexyloxy, n-heptyloxy and n-octyloxy.

[0036]

Examples of the alkoxy moiety in "(difluoroalkoxy)alkyl", "alkoxyalkyl" may include the same as those described above for the "alkoxy".

[0037]

The term "cycloalkyl" may include, for example, mono- to tri-cyclic saturated hydrocarbon group having 3 to 10 carbon atoms. Monocyclic cycloalkyl having 3 to 6 carbon

atoms is preferrable. Specifically, the term may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.1.0]pentyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl.

For the "cycloalkyl" represented by L^1, monocyclic cycloalkyl having 3 to 6 carbon atoms is preferred, and cyclopropyl is more preferrable.

For the "cycloalkyl" moiety in "cycloalkylamino", cyclopropyl is preferrable.

[0038]

The term "aryl" refers to, for example, a mono- to tri-cyclic aromatic hydrocarbon group having 6 to 14 carbon atoms. Specifically, the term may include phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl, 9-anthryl, 1-phenanthryl, 2-phenanthryl, 3-phenanthryl, 4-phenanthryl and 10-phenanthryl. Especially, phenyl is preferrable.

[0039]

The term "heteroaryl" may include, for example, a 5- to 10-membered mono- to bi-cyclic aromatic heterocyclic group having 1 to 4 heteroatoms selected from the group consisting of nitrogen atom, sulfur atom and oxygen atom within the ring. Specifically, the term may include furyl (e.g., 2-furyl and 3-furyl), thienyl (e.g., 2-thienyl and

3-thienyl), pyrrolyl (e.g., 2-pyrrolyl and 3-pyrrolyl), imidazolyl (e.g., 2-imidazolyl and 4-imidazolyl), pyrazolyl (e.g., 3-pyrazolyl and 4-pyrazolyl), triazolyl (e.g., 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl and 1,2,3-triazol-4-yl), tetrazolyl (e.g., 5-tetrazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl and 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl and 4-isoxazolyl and 5-isoxazolyl), oxadiazolyl (e.g., 1,3,4-oxadiazol-2-yl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl and 5-thiazolyl), thiadiazolyl, isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridazinyl (e.g., 3-pyridazinyl and 4-pyridazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl and 5-pyrimidinyl), pyrazinyl (e.g., 2-pyrazinyl), benzimidazolyl (e.g., 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl and 7-benzimidazolyl), indazolyl (e.g., 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl and 7-indazolyl) and isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl and 8-isoquinolyl). Preferably, the heteroaryl may be furyl (e.g., 2-furyl and 3-furyl), imidazolyl (e.g., 2-imidazolyl and 4-imidazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl and 5-thiazolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridazinyl (e.g., 3-pyridazinyl and 4-pyridazinyl), pyrimidinyl (e.g.,

2-pyrimidinyl, 4-pyrimidinyl and 5-pyrimidinyl) or pyrazinyl (e.g., 2-pyrazinyl).

For the "heteroaryl" represented by R^3, 3-pyridyl is preferrable.

For the "heteroaryl" represented by R^8, isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl and 5-isoxazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl and 5-thiazolyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl and 6-pyrimidinyl) and pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl) are preferrable, and 3-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 2-pyrimidinyl and 2-pyridyl are more preferrable.

For the "heteroaryl" represented by L^1, thienyl (e.g., 2-thienyl and 3-thienyl) and pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl) are more preferrable.

[0040]

The term "saturated heterocyclic group" may include, for example, a 3- to 8-membered saturated heterocyclic group having 1 to 3 heteroatoms selected from consisting of nitrogen atom, sulfur atom and oxygen atom within the ring. Specifically, oxetanyl (e.g., 2-oxetanyl and 3-oxetanyl), azetidinyl (e.g., 2-azetidinyl and 3-azetidinyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl and 4-tetrahydropyranyl), pyrrolidinyl

(e.g., 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), piperidinyl (e.g., 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), piperazinyl (e.g., 2-piperazinyl and 3-piperazinyl), morpholinyl (e.g., 2-morpholinyl and 3-morpholinyl), thiomorpholinyl (e.g., 2-thiomorpholinyl and 3-thiomorpholinyl) or tetrahydrofuryl (2-tetrahydrofuryl and 3-tetrahydrofuryl). More preferably, the term may include piperidinyl (e.g., 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), tetrahydrofuryl (2-tetrahydrofuryl and 3-tetrahydrofuryl) and tetrahydropyranyl (2-tetrahydropyranyl and 3-tetrahydropyranyl, 4-tetrahydropyranyl).

For the "saturated heterocyclic group" represented by R^5, 3-pyrrolidinyl, 4-piperidinyl, 3-oxetanyl is preferrable.

Mode for Carrying Out the Invention

[0041]

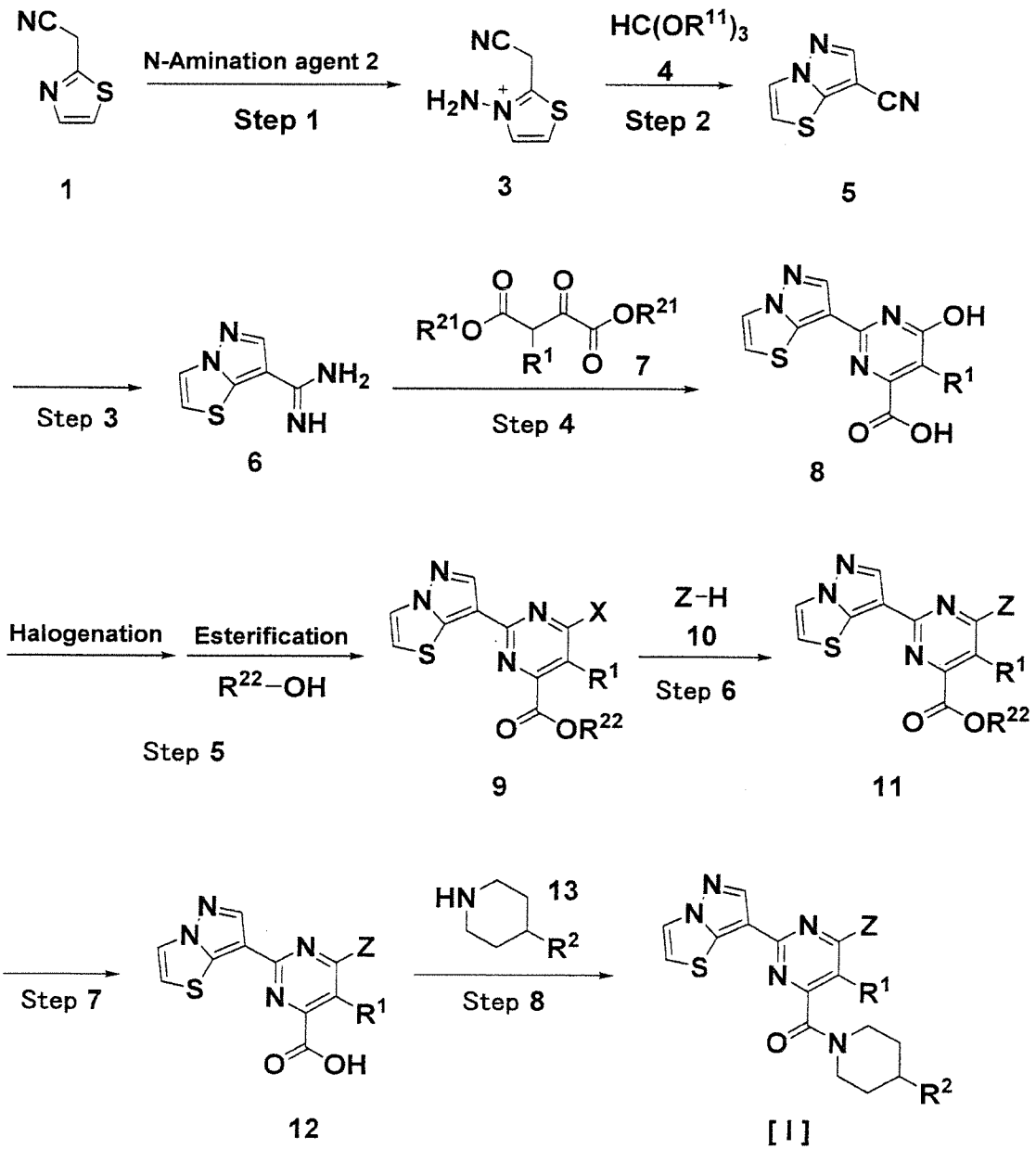
The compound of the invention can be produced according to, for example, the following procedures and examples as described below, or methods known in the art, using a compound or an intermediate, which is available or can be prepared easily. In the case where a starting material has a functional group that may affect the reaction in the process for the production of the compound of the invention, the starting material shold be protected

with an appropriate protective group according to a known method in advance. The protective group can be removed by a known method after the reaction.

[0042]

Scheme 1

[Formula 2]



wherein, Z, R^1 and R^2 are as defined above. R^{11} is alkyl, R^{21} is hydrogen or alkyl, R^{22} is alkyl and X is a leaving group such as halogen.

[0043]

Step 1

The step is an N-amination of the compound 1 (which can be synthesized by using a method as described in, for example, Heterocycles, 2008, 75, 2005-2012.) by using an N-amination agent 2 to give an N-aminothiazolium salt 3.

[0044]

The N-amination agent to be used depends on the solvent employed in the reaction, and examples include but not limited to O-(mesitylenesulfonyl)hydroxyamine.

[0045]

The N-amination agent may be used in an amount of 1 to 5 mole equivalent of the compound 1.

[0046]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and the examples may include, for example, ethers such as tetrahydrofuran (hereinafter referred to as "THF"), diethyl ether, 1,4-dioxane and dimethoxyethane (hereinafter referred to as "DME"), nitriles such as acetonitrile and propionitrile, ketones such as acetone, hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as chloroform, dichloromethane and 1,2-dichloroethane or mixed

solvents thereof.

[0047]

The reaction temperature may be -78 °C to 100 °C, preferably -78 °C to 50 °C.

[0048]

The reaction time may depend on the reaction temperature, and typically, 10 minutes to 24 hours.

[0049]

Step 2

The step is the reaction of the N-aminothiazolium salt 3 with the orthoester compound 4 in an appropriate solvent to obtain the compound 5.

[0050]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and examples of the solvent may include, ethers such as THF, diethyl ether, 1,4-dioxane and DME, nitriles such as acetonitrile and propionitrile, ketones such as acetone, hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as chloroform, dichloromethane and 1,2-dichloroethane or mixed solvents thereof. Alternatively, the orthoester

compound 4 by itself may be used as the solvent in the reaction.

[0051]

The reaction temperature may be 0 °C to 200 °C, preferably 0 °C to 150 °C.

[0052]

The reaction time may depend on the reaction temperature, and typically, 10 minutes to 24 hours.

[0053]

It is preferred that the orthoester compound 4 may be used in an amount of 1 to 50 mole equivalent of the N-aminothiazolium salt 3.

[0054]

Step 3

The step is the conversion of the nitrile to an amidine, which may be conducted according to the procedure as described in, for example, Slee et al., J. Med. Chem. 2008, 51, 1719-1729. That is, the compound 5 is stirred in the presence of a base such as an alkali metal alkoxide in an appropriate solvent to obtain the imidate, and the obtained imidate is reacted with ammonia or an ammonium

salt to give the amidine compound 6.

[0055]

Examples of the base used in the reaction may include alkoxides such as sodium methoxide and sodium ethoxide.

[0056]

It is preferred that the alkoxide may be used in an amount of 1 to 5 mole equivalent of the compound 5.

[0057]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and, typically, an alcohol such as methanol and ethanol may be used.

[0058]

In the preparation of the imidate, the reaction temperature may be 0 °C to 150 °C, preferably 0 °C to 100 °C.

[0059]

In the preparation of the imidate, the reaction time may depend on the reaction temperature, and typically, 30 minutes to 24 hours.

[0060]

In the preparation of the amidine compound 6, examples of the ammonium salt used in the reaction may include ammonium chloride and ammonium acetate.

[0061]

The ammonium salt or ammonia may be used in an amount

of 1 to 10 mole equivalent of the imidate.

[0062]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and, typically, an alcohol such as methanol and ethanol may be used.

[0063]

The reaction temperature may be -78 °C to 150 °C, preferably 0 °C to 150 °C.

[0064]

The reaction time may depend on the reaction temperature, and typically, 30 minutes to 24 hours.

[0065]

The ammonium salt may be added directly to the reaction mixture wherein the imidate has been prepared.

[0066]

Step 4

The step is the reaction of the amidine compound 6 with an oxaloacetic acid compound 7 or a salt thereof in the presence of a base such as potassium hydroxide in an appropriate solvent to obtain the pyrimidine compound 8. The step may be conducted according to the procedure as described in, for example, WO 2009/138712.

[0067]

Examples of the base used in the reaction may include

inorganic bases such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate and cesium carbonate and alkoxides such as sodium methoxide, sodium ethoxide and potassium tert-butoxide.

[0068]

The base may be used in an amount of 1 to 50 mole equivalent of the amidine compound 6.

[0069]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and examples may include, for example, ethers such as THF, 1,4-dioxane and DME, alcohols such as methanol and ethanol, ketones such as acetone, water or mixed solvents thereof.

[0070]

In this reaction, the reaction temperature may be 0 °C to 200 °C, preferably 0 °C to 150 °C.

[0071]

In this reaction, the reaction time may depend on the reaction temperature, and typically, 30 minutes to 24 hours.

[0072]

Step 5

The step is the process to obtain the compound 9 by halogenation of the pyrimidine compound 8 in the presence of a halogenating agent in an appropriate solvent at 0 °C

to 180 °C, followed by esterification of the obtained acid halide.

[0073]

In the halogenation reaction, examples of the halogenating agent may include phosphorus oxychloride, phosphorous oxybromide and phosphorus pentachloride. These halogenating agents may be used alone or in combination thereof in the reaction.

[0074]

In the halogenation reaction, a base is optionally used. Examples of the base used may include diethylaniline, pyridine, 2,6-lutidine, N,N-diisopropylethylamine (hereinafter referred to as "DIPEA") and triethylamine (hereinafter referred to as "TEA").

[0075]

The halogenating agent and the base may be used in an amount of 1 to 100 mole equivalent of the pyrimidine compound 8.

[0076]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and examples may include, ethers such as THF, diethyl ether, 1,4-dioxane and DME, amides such as N,N-dimethylformamide (hereinafter referred to as "DMF"), N,N-dimethylacetamide, N-methylpyrrolidone (hereinafter referred to as "NMP"),

nitriles such as acetonitrile and propionitrile, ketones such as acetone, hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as chloroform, dichloromethane and 1,2-dichloroethane, sulfoxides such as dimethyl sulfoxide (hereinafter referred to as "DMSO") or mixed solvents thereof.

[0077]

The reaction temperature may be 0 °C to 200 °C, preferably 0 °C to 150 °C.

[0078]

The reaction time may depend on the reaction temperature, and typically, 10 minutes to 48 hours.

[0079]

The esterification reaction may be conducted according to a common method. Examples of the alcohol (R^{22}-OH) used in the reaction may include methanol and ethanol.

[0080]

In the esterification reaction, a base is optionally used. Examples of the base used may include organic bases such as diethylaniline, pyridine, 2,6-lutidine, DIPEA and TEA and inorganic bases such as sodium hydrogen carbonate.

[0081]

The alcohol and the base may be used in an amount of 1 to 100 mole equivalent of the acid halide.

[0082]

In the esterification reaction, the solvent to be used in the reaction is not limited unless it is not participated in the reaction, and examples include ethers such as THF, diethyl ether, 1,4-dioxane and DME, amides such as DMF and N,N-dimethylacetamide, nitriles such as acetonitrile and propionitrile, ketones such as acetone, hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as chloroform, dichloromethane and 1,2-dichloroethane, sulfoxides such as DMSO or mixed solvents thereof. Also, the alcohol to be reacted may be used as the solvent.

[0083]

The reaction temperature may be -78 °C to 200 °C, preferably 0 °C to 50 °C.

[0084]

The reaction time may depend on the reaction temperature, and typically, 10 minutes to 48 hours.

[0085]

Step 6

The step is the reaction of the compound 9 with the compound 10 (alcoholic compound R^3OH or amine compound NHR^4R^5) in an appropriate solvent to obtain the compound 11.

[0086]

In the reaction, the compound 10 may be used in an

amount of 1 to 10 mole equivalent of the compound 9.

[0087]

The reaction may be conducted in the presence of an acid or a base, as necessary. Examples of the acid used may include, inorganic acids such as hydrochloric acid and sulfuric acid. Examples of the base used may include organic bases such as TEA, DIPEA, N,N-dimethylaniline, pyridine, DMAP and 1,8-diazabicyclo[5.4.0]-7-undecen, inorganic bases such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate and cesium carbonate, alkoxides such as sodium methoxide, sodium ethoxide and potassium tert-butoxide, and alkali metal hydrides such as sodium hydride and potassium hydride.

[0088]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and examples include ethers such as THF, diethyl ether, 1,4-dioxane and DME, nitriles such as acetonitrile and propionitrile, ketones such as acetone, halogenated hydrocarbons such as chloroform, dichloromethane and 1,2-dichloroethane, hydrocarbons such as toluene, benzene and cyclohexane, alcohols such as methanol, ethanol, isopropylalcohol and butanol, amides such as DMF, N,N-dimethylacetamide, and NMP, sulfoxides such as DMSO or mixed solvents thereof.

[0089]

In this reaction, the reaction temperature may be 0 °C to 200 °C, preferably 0 °C to 150 °C. If necessary, the reaction may be conducted by using microwave or in the closed condition.

[0090]

The reaction time may depend on the type of starting materials and the base and the reaction temperature, and typically, 30 minutes to 48 hours.

[0091]

Step 7

The step is hydrolysis reaction of the ester compound 11 in the presence of an appropriate acid or base in an appropriate solvent to obtain the carboxylic acid 12.

[0092]

In the reaction, examples of the acid used may include inorganic acids such as hydrochloric acid and sulfuric acid and organic acids such as trifluoroacetic acid (hereinafter referred to as "TFA"), methanesulfonic acid and toluenesulfonic acid. Examples of the base may include inorganic bases such as sodium hydroxide, potassium hydroxide and lithium hydroxide.

[0093]

In the reaction, the acid or base may be used in an amount of 1 to 10 mole equivalent of the ester compound 11.

[0094]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and examples include water, alcohols such as methanol, ethanol and isopropanol, ethers such as THF, diethyl ether, 1,4-dioxane and DME, nitriles such as acetonitrile and propionitrile, ketones such as acetone or mixed solvents thereof.

[0095]

In this reaction, the reaction temperature may be -78 °C to 200 °C, preferably 0 °C to 100 °C.

[0096]

The reaction time may depend on the reaction temperature, and typically, 30 minutes to 48 hours.

[0097]

Step 8

The step is the condensation reaction of the carboxylic acid 12 and the compound 13 in an appropriate solvent to obtain compound [I]. The compound [I] can be prepared by reacting the carboxylic acid 12 or its reactive derivative with the compound 13.

[0098]

Examples of the reactive derivatives of the carboxylic acid 12 may include, those commonly used in the amide condensation formation reaction such as acid halides (e.g., acid chloride and acid bromide), mixed anhydrides,

imidazolides and reactive amides.

[0099]

When using the carboxylic acid 12, a condensing agent such as 1,1'-carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (hereinafter referred to as "WSCD (Water Soluble Carbodiimide)"), N,N'-dicyclohexylcarbodiimide (hereinafter referred to as "DCC"), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (hereinafter referred to as "HATU"), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (hereinafter referred to as "HBTU"), diethyl cyanophosphonate, diphenylphosphoryl azide, 2-chloro-1-methylpyridinium iodide, 1H-benzotriazol-1-yloxytripyrrolizinophosphonium hexafluorophosphate or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate) can be used.

[0100]

In the reaction, the condensing agent may be used in an amount of 1 to 3 mole equivalent of the carboxylic acid 12.

[0101]

The reaction may be conducted in the presence of a base, as necessary. Examples of the base used may include, for example, organic bases such as TEA, DIPEA, N,N-dimethylaniline, pyridine, DMAP and 1,8-

diazabicyclo[5.4.0]-7-undecene.

[0102]

An additive such as 1-hydroxybenzotriazole (hereinafter referred to as "HOBt") and N-hydroxysuccinimide can be added to the reaction.

[0103]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and examples include ethers such as THF, diethyl ether, 1,4-dioxane and DME, amides such as DMF and N,N-dimethylacetamide, nitriles such as acetonitrile and propionitrile, ketones such as acetone, hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as chloroform and dichloromethane or mixed solvents thereof.

[0104]

The reaction temperature may be -78 °C to 200 °C, preferably -20 °C to 50 °C.

[0105]

The reaction time may depend on the type of starting materials and condensing agents and the reaction temperature, and typically, 10 minutes to 24 hours.

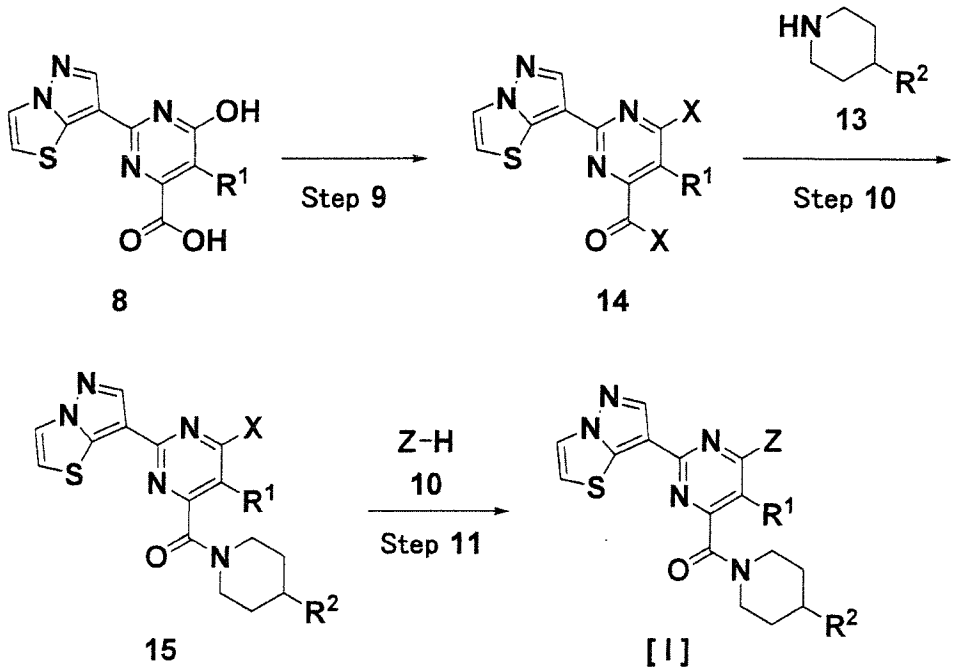
[0106]

The compound [I] also may be prepared according to the following Scheme 2.

[0107]

Scheme 2

[Formula 3]



wherein, Z, R^1 and R^2 are as defined above. X is halogen.

[0108]

Step 9

The step is halogenation reaction of the hydroxide moiety of the compound 8 with a halogenating agent, such as phosphorus oxychloride in an appropriate solvent, to obtain the acid halide 14. The step may be conducted as described in Step 5

[0109]

Step 10

The step is a reaction of the acid halide 14 with the amine compound 13 in an appropriate solvent to obtain the

amide compound 15.

[0110]

In the reaction, the compound 13 may be used in an amount of 1 to 3 mole equivalent of the compound 14.

[0111]

The reaction may be conducted in the presence of a base, as necessary. Examples of the base used may include the organic bases such as TEA, DIPEA, N,N-dimethylaniline, pyridine, DMAP and 1,8-diazabicyclo[5.4.0]-7-undecene and inorganic bases such as sodium hydrogen carbonate, sodium carbonate, potassium carbonate and cesium carbonate.

[0112]

The solvent to be used in the reaction is not limited unless it is not participated in the reaction, and examples include ethers such as THF, diethyl ether, 1,4-dioxane and DME, nitriles such as acetonitrile and propionitrile, ketones such as acetone, halogenated hydrocarbons such as chloroform, dichloromethane and 1,2-dichloroethane, hydrocarbons such as toluene, benzene and cyclohexane, amides such as DMF and N,N-dimethylacetamide, sulfoxides such as DMSO or mixed solvents thereof.

[0113]

In this reaction, the reaction temperature may be -50 °C to 100 °C, preferably 0 °C to 50 °C.

[0114]

The reaction time may depend on the type of starting materials and bases and the reaction temperature, and typically, 5 minutes to 48 hours.

[0115]

Step 11

The step is a reaction of the compound 15 with the compound 10 (an alcohol compound R^3OH or an amine compound R^4R^5NH) in an appropriate solvent to obtain the compound [I]. The step may be conducted as described in the above Step 6.

[0116]

The pyrazolothiazole compound of the invention can be used as a medicine as it is, and also may be modified and used in a form of a pharmaceutically acceptable salt, a solvate or a solvate of salt by using a well-known method. Examples of the pharmaceutically acceptable salt may include, for example, a salt with a mineral acid such as hydrochlorate, hydrobromate, sulfate and phosphate, and a salt with an organic salt such as acetate, citrate, tartarate, maleate, succinate, fumarate, p-toluenesulfonate, benzenesulfonate and methanesulfonate.

[0117]

The solvate includes a solvate with an organic solvent and a hydrate. Examples of the pharmaceutically acceptable solvate may include, for example, alcoholate (e.g.,

ethanolate) and hydrate. The hydrate may include for example, monohydrate and dihydrate. The solvate is formed by coordination with any type and number of solvents. The pharmaceutically acceptable salt may form a solvate.

[0118]

For example, a hydrochloride salt of the compound can be obtained by dissolving the pyrazolothiazole compound of the invention in a solution of hydrogen chloride in alcohol, a solution of hydrogen chloride in ethyl acetate, a solution of hydrogen chloride in 1,4-dioxane or a solution of hydrogen chloride in diethyl ether.

[0119]

Some of the compounds of the present invention may have an asymmetric carbon, and the respective stereo isomers and mixtures thereof are all included in the present invention. The stereo isomers can be prepared, for example, by means of optical resolution from the racemate thereof according to a known method using an optically active acid (e.g., tartaric acid, dibenzoyltartaric acid, mandelic acid and 10-camphor sulfonic acid, etc.), or by using an optically active compound prepared in advance as a starting material. In addition, the stereo isomers may be prepared by optical resolution using a chiral column or by asymmetric synthesis. Also, some of the compounds of the present invention may form tertmers, and the respective

tautomers and mixtures thereof are also included in the invention.

[0120]

The compound of the invention has JAK1 inhibitory activity as shown in the following test examples. Further, the compound of the invention also has anti-inflammatory, immunosuppressive and anti-proliferative effects etc., based on their JAK1 inhibitory activity.

[0121]

Accordingly, the compound of the invention can be used as a preventive or therapeutic agent, for example, for the diseases associated with JAK1 and also the diseases for which the effect of the compound is expected in view of its anti-inflammatory, immunosuppressive and anti-proliferative effects etc.

Examples of specific diseases for which the compound of the invention can be applied include autoimmune disease (e.g., rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, Castleman's disease, systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, inflammatory bowel disease, Behçet's disease, myasthenia gravis, type 1 diabetes mellitus, immunoglobulin nephropathy, autoimmune thyroid diseases, psoriasis, scleroderma, lupus nephritis, dry eye, vasculitis (e.g., Takayasu's arteritis, giant cell arteritis, microscopic

polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis), dermatomyositis and polymyositis and neuromyelitis optica), inflammatory diseases (e.g., atopic dermatitis, contact dermatitis, eczema, pruritus, food allergies, bronchial asthma, eosinophilic pneumonia, chronic obstructive pulmonary disease, allergic rhinitis, chronic sinusitis, eosinophilic sinusitis, nasal polyp, allergic conjunctivitis, osteoarthritis, ankylosing spondylitis, Kawasaki disease, Buerger's disease, polyarteritis nodosa and IgA vasculitis), proliferative diseases (e.g., solid cancers, blood cancers, lymph malignant tumor, myeloproliferative diseases, multiple myeloma, pulmonary fibrosis and eosinophilia), sudden hearing loss, diabetic nephropathy, alopecia areata, bone marrow transplant rejection or organ transplant rejection.

[0122]

The compound of the invention may be administered as a medicament to mammals, including human, as it is or as a pharmaceutical composition containing the same in an amount of, for example, 0.001 % to 99.5 %, preferably 0.1 % to 90 %, in combination with one or more pharmaceutically acceptable nontoxic and inactive carrier(s).

[0123]

The carrier may be one or more selected from solid, semi-solid, or liquid diluents, fillers, and other auxiliaries for pharmaceutical formulation is used. The pharmaceutical composition according to the invention may be administered in a unit dosage form. The pharmaceutical composition may be administered by interstitial, oral, intravenous, topical (e.g., transdermal, instillation, intraperitoneal or intrathoracic administration) or transrectal administration. The composition should be administered in a dosage form suitable for these administration methods.

[0124]

The dose of the compound should be adjusted taking into account the conditions of the patient, such as age, body weight, and the disease to be treated and the stage of the disease, the route of administration, and the compound to be administered, the type of salt in case where the compound is a salt, etc.. In the case of oral administration to an adult, a typical daily dose of the compound of the invention or its pharmaceutically acceptable salt may be 0.01 mg to 5 g, and preferably 1 mg to 500 mg. In some cases, a lower dose may be sufficient, or conversely, or a higher dose may be required. In general, the dose is given once a day or several times per day as divided portions, or in the case of intravenous

administration, the medicine can be a bolus injection or continuously administered within 24 hours.

[0125]

One or more of hydrogen, carbon and/or other atoms in the compound of the invention can be replaced with the respective isotope of hydrogen, carbon and/or other atoms. Examples of such isotopes include those of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{123}I and ^{36}Cl. A compound substituted with such isotope may be useful as a medicament, and all of such radiolabeled forms of the compound are inclued in the invention.

Examples

[0126]

The invention is described in more detail with reference to the following Examples, Test Examples and Formulation Examples, which are not intended to limit the scope of the present invention.

[0127]

The abbreviations used in the Examples are as follows.

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

DIPEA: N,N-diisopropylethylamine

TEA: triethylamine

THF: tetrahydrofuran

TFA: trifluoroacetic acid

NMP: N-methylpyrrolidone

HATU: O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

$CDCl_3$: deuterochloroform

DMSO-d6: hexadeuteroddimethyl sulfoxide

MS: mass spectrometry

LCMS: high-pressure liquid chromatograph mass spectrometry

ESI: electron spray ionization

M: molar concentration

[0128]

MS was determined by using LCMS. ESI method was used as the ionization method. The measurements of the mass spectrometry are shouwn as m/z.

The measurement condition for LCMS is as follows.

Analyzer: ACQUITY UPLC MS/PDA system (Waters)

Mass spectrometer: Waters 3100 MS detector

Photodiode array detector: ACQUITY PDA detector (UV

Detection wavelength: 210 to 400nm)

Column: Acquity BEH C_{18}, 1.7μm, 2.1 x 50mm

Flow rate: 0.5mL/min

Column temperature: 40 °C

Solvent;

Solution A: 0.1 % formic acid/H_2O (v/v; the same hereinafter)

Solution B: 0.1 % formic acid/acetonitrile

[0129]

The microwave experiment was done using Biotage Initiator 60™, which is able to achive a temperature from 40 to 250 °C and a pressure up to 20 bar. As used herein, the specific optical rotation ($[\alpha]_D$) means a specific optical rotation measured by a polarimeter, such as HORIBA high-speed automatic polarimeter SEPA-500.

[0130]

Reference Example 1: Pyrazolo[5,1-b][1,3]thiazole-7-carbonitrile

[Step 1] Preparation of 2-(thiazol-2-yl)acetonitrile

To a solution of tert-butyl cyanoacetate (28 g) in DMF (100 mL) was added 60 % sodium hydride (7.9 g) in portions under ice cooling, and the resulting mixture was stirred for 10 min. To the mixture was added 2-bromothiazole (25g), and the mixture was stirred at room temperature for 15 min, then at 120 °C for 2 h. To the reaction mixture was added 1 M aqueous solution of hydrochloric acid, and the aqueous

layer was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was washed with hexane, the resulting solid was suspended in toluene (200 mL), to the suspension was added para-toluenesulfonic acid monohydrate (2.0g), and the mixture was stirred at 105 °C for 2 h. The reaction solution was diluted with ethyl acetate, and the liquid separation was carried by an addition of saturated aqueous sodium bicarbonate solution. The aqueous layer was further extracted with ethyl acetate and the combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (7.0 g).

MS (m/z): 125 $[M+H]^+$

[0131]

[Step 2] Preparation of pyrazolo[5,1-b][1,3]thiazole-7-carbonitrile

To a solution of 2-(thiazol-2-yl)acetonitrile obtained in Step 1 (5 g) in dichloromethane (50 mL) was added a solution of O-(mesitylsulfonyl)hydroxyamine (which can be prepared according to the method described in, for example, Organic Process Research & Development, 2009, 13, 263-267.)

in dichloromethane (20 mL) under ice cooling, and the mixture was stirred at room temperature for 2 h. Under ice cooling, to the reaction mixture was added diethyl ether, and the precipitated solid was collected on a filter. The resulting solid was suspended in triethyl orthoformate (35 mL), and the mixture was stirred at 120 °C for 1 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (2.5 g).
MS (m/z): 150 $[M+H]^+$

[0132]

Reference Example 2: 6-Hydroxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

To a solution of pyrazolo[5,1-b][1,3]thiazole-7-carbonitrile obtained in Reference Example 1 (6 g) in methanol (150 mL) was added a solution of 28 % sodium methoxide in methanol (24.6 mL), and the mixture was stirred at room temperature for 3 h. Then, ammonium chloride (12.9 g) was added thereto, and the mixture was stirred at 90 °C for 1 h. The reaction solution was concentrated under reduced pressure, to the resulting residue was added a solution of sodium diethyl oxalacetate (33.8g) in 5 M aqueous sodium hydroxide solution(200 mL), and the mixture was stirred at 100 °C overnight. To the

reaction mixture was added conc. hydrochloric acid to make the solution acidic, and the precipitated solid was collected on a filter. The resulting solid was dissolved in 5 M aqueous potassium hydroxide solution, and was washed with chloroform. To the aqueous layer was added conc. hydrochloric acid to make the solution acidic, the precipitated solid was collected on a filter, and dried to obtain the title compound (10 g).

MS (m/z): 263 $[M+H]^+$

[0133]

Reference Example 3: Methyl 6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-carboxylate

6-Hydroxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 2 (1.4g) was suspended in phosphorus oxychloride (20 mL), to the suspension was added diethylaniline (1.6g), and the mixture was stirred at 130 °C for 2 h. The reaction solution was concentrated under reduced pressure, to the reaction mixture was added methanol (100 mL) under ice cooling, and the resulting mixture was stirred at 10 min. The reaction solution was diluted with chloroform, separated by adding water, and the aqueous layer was further extracted with chloroform. The combined organic layer was dried over anhydrous magnesium sulfate, and

concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (910 mg).

MS (m/z): 297 $[M+H]^+$

[0134]

Reference Example 4: 6-Hydroxy-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

To a solution of pyrazolo[5,1-b][1,3]thiazole-7-carbonitrile obtained in Reference Example 1 (300 mg) in methanol (6 mL) was added a solution of 28 % sodium methoxide in methanol (0.41 mL), and the mixture was stirred at room temperature for 1 h. Then, ammonium chloride (215 mg) was added thereto, and the mixture was stirred at 70 °C for 2 h. The reaction solution was concentrated under reduced pressure, the resulting residue was dissolved in 5 M aqueous sodium hydroxide solution(1.2 mL) and water (7 mL), methyloxalacetic acid diethyl ester (611 mg) was added to the solution, and the mixture was stirred at 90 °C for 45 min. To the reaction mixture was added conc. hydrochloric acid to make the solution acidic, the precipitated solid was collected on a filter, and dried to obtain the title compound (166 mg).

MS (m/z): 277 $[M+H]^+$

[0135]

Reference Example 5: Methyl 6-chloro-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-carboxylate

Analogous to the method in Reference Example 3, the title compound was synthesized by using 6-hydroxy-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 4 in place of 6-hydroxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid.

MS (m/z): 311 $[M+H]^+$

[0136]

Reference Example 6: (2S)-1-(Difluoromethoxy)propan-2-amine hydrochloride

[Step 1] Preparation of benzyl N-[(2S)-1-(difluoromethoxy)propan-2-yl]carbamate

Under argon atmosphere, to a solution of benzyl [(1S)-1-(hydroxymethyl)ethyl]carbamate (2g) in acetonitrile (40 mL) were added 2,2-difluoro-2-(fluorosulfonyl)acetic acid (2.6g) and copper iodide (364 mg), and the mixture was stirred at 50 °C for 1 h 30 min. The reaction solution was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate,

and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (1.3 g).

^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d), 3.75-3.90 (2H, m), 4.00 (1H, bs), 4.82 (1H, bs), 5.11 (2H, s), 6.22 (1H, t), 7.30-7.40 (5H, m)

[0137]

[Step 2] Preparation of (2S)-1-(difluoromethoxy)propan-2-amine hydrochloride

To a solution of benzyl N-[(2S)-1-(difluoromethoxy)propan-2-yl]carbamate obtained in Step 1 (1.3 g) in ethanol (40 mL) was added 20 % palladium hydroxide (on activated carbon, 300 mg), and the medium pressure catalytic reduction was conducted. The reaction mixture was filtered to remove the palladium, then 4 M hydrogen chloride-ethyl acetate solution (2 mL) was added to the mother liquid, and the solvent was concentrated under reduced pressure to give the title compound (668 mg).

^{1}H-NMR (DMSO-d6) δ: 1.19 (3H, d), 3.40-3.50 (1H, m), 3.86 (1H, dd), 3.97 (1H, dd), 6.77 (1H, t), 8.06 (3H, bs)

[0138]

Reference Example 7: (1S,2S)-2-(Difluoromethoxy)cyclopentanamine hydrochloride

[Step 1] Preparation of benzyl N-[(1S,2S)-2-hydroxycyclopentyl]carbamate

To a solution of (1S,2S)-2-benzyloxycyclopentanamine (5.0 g) in ethanol (40 mL) was added 20 % palladium hydroxide (on activated carbon, 1.0 g), and the medium pressure catalytic reduction was conducted. Palladium was filtered off, and the solvent was concentrated under reduced pressure. To the resulting residue were added water (100 mL) and sodium carbonate (7.0 g), then benzyl chloroformate (6.7 g) was added thereto under ice cooling, and the mixture was stirred at room temperature overnight. The reaction mixture was extracted with chloroform, and the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (5.9 g). MS (m/z): 236 $[M+H]^+$

[0139]

[Step 2] Preparation of benzyl N-[(1S,2S)-2-(difluoromethoxy)cyclopentyl]carbamate

Analogous to the method in Reference Example 6 Step 1, the title compound was synthesized by using benzyl N-[(1S,2S)-2-hydroxycyclopentyl]carbamate obtained in Step 1 in place of benzyl [(1S)-1-(hydroxymethyl)ethyl]carbamate.

^{1}H-NMR ($CDCl_3$) δ: 1.40-1.50 (1H, m), 1.62-1.88 (3H, m), 1.91-2.05 (1H, m), 2.10-2.25 (1H, m), 3.95-4.00 (1H, m), 4.40 (1H, bs), 4.72 (1H, bs), 5.10 (2H, dd), 6.33 (1H, t), 7.30-7.41 (5H, m)

[0140]

[Step 3] Preparation of (1S,2S)-2-(difluoromethoxy)cyclopentanamine hydrochloride

Analogous to the method in Reference Example 6 Step 2, the title compound was synthesized by using benzyl N-[(1S,2S)-2-(difluoromethoxy)cyclopentyl]carbamate obtained in Step 2 in place of benzyl N-[(2S)-1-(difluoromethoxy)propan-2-yl]carbamate.

^{1}H-NMR (DMSO-d6) δ: 1.50-1.78 (4H, m), 2.01-2.10 (2H, m), 3.48 (1H, bs), 4.55 (1H, bs), 6.78 (1H, t), 8.28 (3H, bs)

[0141]

Reference Example 8: {1-[(Difluoromethoxy)methyl]cyclopropyl}methanamine

To a solution of [1-(aminomethyl)cyclopropyl]methanol (720 mg) in dichloromethane (15 mL) was added DIPEA (2.5 mL), then benzyl chloroformate (1.46 g) was added thereto under ice cooling, and the mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, and the resulting

residue was purified by silica gel column chromatography to give an oil (348 mg). To a solution of this oil (348 mg) in acetonitrile (10 mL) were added 2,2-difluoro-2-(fluorosulfonyl)acetic acid (395 mg) and copper iodide (56 mg), and the mixture was stirred at 50 °C for 1 h. The reaction solution was separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give an oil (129 mg). To a solution of the oil (129 mg) in methanol (8.0 mL) was added 20 % palladium hydroxide (on activated carbon, 43 mg), and the medium pressure catalytic reduction was conducted. The reaction solution was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give the title compound (68 mg).

^{1}H-NMR ($CDCl_3$) δ: 0.51-0.52 (4H, m), 2.69 (2H, s), 3.79 (2H, s), 6.25 (1H, t)

[0142]

Reference Example 9: {1-[(Difluoromethoxy)methyl]cyclobutyl}methanamine

Analogous to the method in Reference Example 8, the

title compound was synthesized by using [1-(aminomethyl)cyclobutyl]methanol (which is prepared according to the method described in, for example, Journal of Medicinal Chemistry, 1972, 15, 1003-1006) in place of [1-(aminomethyl)cyclopropyl]methanol.

^{1}H-NMR ($CDCl_3$) δ: 1.78-1.91 (6H, m), 2.78 (2H, s), 3.86 (2H, s), 6.23 (1H, t)

[0143]

Reference Example 10: {1-[(Difluoromethoxy)methyl]cyclopentyl}methanamine

Analogous to the method in Reference Example 8, the title compound was synthesized by using [1-(aminomethyl)cyclopentyl]methanol (which is prepared according to the method described in, for example, Journal of Medicinal Chemistry, 1972, 15, 1003-1006) in place of [1-(aminomethyl)cyclopropyl]methanol.

^{1}H-NMR ($CDCl_3$) δ: 1.42-1.46 (4H, m), 1.58-1.64 (4H, m), 2.69 (2H, s), 3.72 (2H, s), 6.24 (1H, t)

[0144]

Reference Example 11: {4-[(Difluoromethoxy)methyl]tetrahydro-2H-pyran-4-yl}methanamine

To a solution of ethyl 4-{[(tert-

butoxycarbonyl)amino]methyl}tetrahydro-2H-pyran-4-carboxylate (1.3 g) in dichloromethane (10 mL) was added TFA (5.0 mL), and the mixture was stirred at room temperature for 4 h. The reaction solution was concentrated under reduced pressure, to a solution of the resulting residue in dichloromethane (10 mL) was added DIPEA (3.1 mL), then benzyl chloroformate (1.1 g) was added thereto under ice cooling, and the mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give an oil (1.4 g). To a solution of the oil (1.3 g) in ethanol (20 mL) was added sodium borohydride (382 mg) under ice cooling, and the mixture was stirred at room temperature for 2.5 days. Then, sodium borohydride (382 mg) was added thereto, the mixture was stirred at room temperature for 4 h, then at 50 °C for 3 h, and further at room temperature overnight. To the reaction solution was added water under ice water cooling, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give an oil (484 mg). To a solution of the oil (484 mg) in acetonitrile (10 mL) were added 2,2-

difluoro-2-(fluorosulfonyl)acetic acid (463 mg) and copper iodide (66 mg), and the mixture was stirred at 50 °C for 1 h. To the reaction solution was added saturated aqueous sodium bicarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give an oil (209 mg). To a solution of the oil (200 mg) in methanol (8.0 mL) was added 20 % palladium hydroxide (on activated carbon, 80 mg), and the medium pressure catalytic reduction was conducted. The reaction mixture was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give the title compound (108 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.50-1.53 (4H, m), 2.76 (2H, s), 3.64-3.71 (4H, m), 3.84 (2H, s), 6.24 (1H, t)

[0145]

Reference Example 12: (2R)-N,3,3-Trimethylbutan-2-amine hydrochloride

To a solution of (2R)-3,3-dimethylbutan-2-amine (5.0 g) in dichloromethane (100ml) was added TEA (15ml), benzyl chloroformate (9.3 g) was added dropwise thereto under ice cooling, and the mixture was stirred overnight. The

reaction mixture was diluted with chloroform, the solution was separated by adding saturated aqueous sodium bicarbonate solution, the aqueous layer was further extracted with chloroform, and the combined organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the crude product (4.0 g). To a solution of the obtained crude product (4.0 g) in DMF (15ml) was added iodomethane (4.8 g), and 60 % sodium hydride (748 mg) was added thereto under ice cooling. After the mixture was stirred at room temperature for 1 h, ice water was added thereto and the reaction solution was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the crude product (4.2 g). To a solution of the obtained crude product (4.2 g) in ethanol (20 mL) was added 20 % palladium hydroxide (on activated carbon, 1.0 g), and the medium pressure catalytic reduction was conducted. The reaction mixture was filtered to remove the palladium, 2 M hydrogen chloride-ethanol solution (9.0ml) was added to the mother liquid, and the solvent was

concentrated under the reduced pressure to give the title compound (2.0 g).

MS (m/z): 116 $[M-Cl]^+$

[0146]

Reference Example 13: 1-[1-(Methoxymethyl)cyclopropyl]-N-methylmethanamine hydrochloride

[Step 1] Preparation of benzyl {[1-(hydroxymethyl)cyclopropyl]methyl}carbamate

To a solution of [1-(aminomethyl)cyclopropyl]methanol (1.5 g) (which was prepared analogous to the method described in, for example, Journal of Medicinal Chemistry, 1972, 15, 1003-1006) in dichloromethane (30 mL) was added DIPEA (3.7 g), benzyl chloroformate (3.5 g) was added thereto under ice cooling, and the mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (3.0 g).

^{1}H-NMR ($CDCl_3$) δ: 0.46 (4H, s), 2.78 (1H, t), 3.20 (2H, d), 3.40 (2H, d), 5.12 (2H, s), 5.23 (1H, s), 7.35-7.37 (5H, m)

[0147]

[Step 2] Preparation of benzyl {[1-(methoxymethyl)cyclopropyl]methyl}methylcarbamate

To a solution of benzyl {[1-(hydroxymethyl)cyclopropyl]methyl}carbamate obtained in Step 1 (350 mg) in DMF (3.0 mL) were added iodomethane (1.0 g) and silver oxide (1.7 g), and the mixture was stirred at room temperature overnight. Under ice cooling, to the reaction mixture was added saturated aqueous aqueous ammonium chloride, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (189 mg).
^{1}H-NMR ($CDCl_3$) δ: 0.46-0.60 (4H, m), 2.99 (3H, s), 3.15-3.36 (7H, m), 5.13 (2H, s), 7.28-7.39 (5H, m)

[0148]

[Step 3] Preparation of 1-[1-(methoxymethyl)cyclopropyl]-N-methylmethanamine hydrochloride

To a solution of benzyl {[1-(methoxymethyl)cyclopropyl]methyl}methylcarbamate obtained in Step 2 (165 mg) in ethanol (6.0 mL) was added palladium hydroxide (on activated carbon, 80 mg), and the medium pressure catalytic reduction was conducted. The reaction mixture was filtered to remove the palladium, 2 M hydrogen chloride-ethanol solution (27 μL) was added to the mother liquid, and the solvent was concentrated under reduced

pressure to give the title compound (95 mg).

^{1}H-NMR (DMSO-d6) δ: 0.53 (2H, t), 0.66 (2H, t), 2.51 (3H, s), 2.88 (2H, s), 3.26 (3H, s), 3.27 (2H, s), 8.52 (2H, br)

[0149]

Reference Example 14: Methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

[Step 1] Preparation of methyl piperidin-4-ylcarbamate

To a solution of 1-benzylpiperidin-4-amine (5.0 g) in dichloromethane (100 mL) was added TEA (9.2 mL) methyl chloroformate (2.6 g) was added dropwise thereto under ice cooling, and the mixture was stirred for 1 h. The reaction solution was diluted with chloroform, separated by adding water, and the aqueous layer was further extracted with chloroform. The combined organic layer was dried over anhydrous magnesium sulfate, and then, concentrated under reduced pressure to give an oil (3.4 g). To a solution of the resulting an oil (3.4 g) in ethanol (50 mL) was added 20 % palladium hydroxide (on activated carbon, 1 g), and the medium pressure catalytic reduction was conducted. The reaction mixture was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give the title compound (1.9 g).

MS (m/z): 159 $[M+H]^+$

[0150]

[Step 2] Preparation of methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

6-Hydroxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 2 (700 mg) was suspended in phosphorus oxychloride (5.0 mL), diethylaniline (0.4 g) was added to the suspension, and the mixture was stirred at 110 °C for 2 h. The reaction solution was concentrated under reduced pressure, and it is dissolved in dichloromethane (40 mL) under ice cooling. To the resulting solution were added DIPEA (2.3 mL) and methyl piperidin-4-ylcarbamate obtained in Step 1 (443 mg), and the mixture was stirred at room temperature for 30 min. The reaction solution was diluted with chloroform, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with chloroform. The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (570 mg).

MS (m/z): 421, 423 $[M+H]^+$

[0151]

Reference Example 15: N-(1-{[6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using N-(piperidin-4-yl)cyclopropanecarboxamide (which was prepared analogous to the method described in, for example, Journal of Medicinal Chemistry, 2010, 53, 6386-6397) in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 431, 433 $[M+H]^+$

[0152]

Reference Example 16: N-(1-{[6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methylpropanamide

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using 2-methyl-N-(4-piperidyl)propanamide (which was prepared analogous to the method described in, for example, Bioorganic & Medicinal Chemistry Letters, 2012, 22, 3157-3162) in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 433, 435 $[M+H]^+$

[0153]

Reference Example 17: tert-Butyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using tert-butyl N-(4-piperidyl)carbamate in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 463, 465 $[M+H]^+$

[0154]

Reference Example 18: [6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyridin-2-ylamino)piperidin-1-yl]methanone

Under argon atmosphere, to a solution of 1-benzylpiperidin-4-amine (980 mg) and 2-fluoropyridine (500 mg) in THF (3.0 mL) was added 1 M lithium bis(trimethylsilyl)amide (THF solution, 10.3 mL) at -78 °C. The mixture was stirred at room temperature for 1h, then at 70 °C overnight. The reaction mixture was diluted with chloroform, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with chloroform. The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give an oil (155 mg).

To a solution of the resulting oil (150 mg) in ethanol (10 mL) were added 20 % palladium hydroxide (on activated carbon, 50 mg) and TFA (1 drop), and the medium pressure catalytic reduction was conducted at 40 °C. The reaction mixture was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give a solid (110 mg). 6-Hydroxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 2 (150 mg) was suspended in phosphorus oxychloride (1.1 mL), diethylaniline (85 mg) was added to the suspension, and the mixture was stirred at 110 °C for 2 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was dissolved in dichloromethane (10 mL) under ice cooling, DIPEA (0.5 mL) and the above solid (101 mg) were added to the solution, and the mixture was stirred at room temperature for 30 min. The reaction solution was diluted with chloroform, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with chloroform. The combined organic layers were dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (36 mg).

MS (m/z): 400, 402 $[M+H]^+$

[0155]

Reference Example 19: [6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone

Under argon atmosphere, to a solution of tert-butyl N-thiazol-2-ylcarbamate (1.9 g) and tert-butyl 4-hydroxypiperidine-1-carboxylate (1.8 g) in THF (20 mL) was added diethyl azodicarboxylate (2.2 M toluene solution, 5.1 mL) under ice cooling, and the mixture was stirred at room temperature for 16 h. The solvent was distilled off, and the resulting residue was purified by silica gel column chromatography to give a solid 1 (2.2 g). To a solution of the obtained solid 1 (2.2 g) in dichloromethane (5 mL) was added TFA (5 mL), and the mixture was stirred at room temperature for 1 h 30 min. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give a solid 2 (796 mg). 6-Hydroxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 2 (100 mg) was suspended in phosphorus oxychloride (1.1 mL), diethylaniline (57 mg) was added to the suspension, and the mixture was stirred at 110 °C for 2 h. The reaction solution was concentrated under reduced pressure, the concentrate was dissolved in dichloromethane (10 mL) under ice cooling, DIPEA (0.33 mL) and the solid 2

(136 mg) were added to the solution, and the mixture was stirred at room temperature for 30 min. The reaction solution was diluted with chloroform, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with chloroform. The combined organic layers were dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (70 mg).
MS (m/z): 446, 448 $[M+H]^+$

[0156]

Reference Example 20: [6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyrimidin-2-ylamino)piperidin-1-yl]methanone

To a solution of tert-butyl 4-(pyrimidin-2-ylamino)piperidine-1-carboxylate (251 mg) in dichloromethane (3.0 mL) was added TFA (1.0 mL), and the mixture was stirred at room temperature for 30 min. The solvent was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give a solid (248 mg). 6-Hydroxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 2 (100 mg) was suspended in phosphorus oxychloride (1.1 mL), diethylaniline (57 mg)

was added to the suspension, and the mixture was stirred at 110 °C for 1 h. The reaction solution was concentrated under reduced pressure, the resulting residue was dissolved in dichloromethane (10 mL) under ice cooling, DIPEA (0.33 mL) and the solid (134 mg) were added to the solution and the mixture was stirred at room temperature for 30 min. The reaction solution was diluted with chloroform, separated by adding saturated aqueous sodium bicarbonate water, and the aqueous layer was further extracted with chloroform. The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (104 mg). MS (m/z): 441, 443 $[M+H]^+$

[0157]

Reference Example 21: Cyclopropyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

[Step 1] Preparation of benzyl 4-(cyclopropanecarbonylamino)piperidine-1-carboxylate

To a solution of 1-benzyloxycarbonylpiperidin-4-carboxylic acid (400 mg) in toluene (3 mL) were added TEA (0.85 mL) and diphenylphosphoryl azide (627 mg), and the mixture was stirred at 90 °C for 3h. Then, cyclopropanol

(132 mg) (which was prepared analogous to the method described in, for example, US2012/0010183) was added thereto, and the mixture was stirred at 80 °C overnight. The reaction mixture was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate water, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (190 mg).
MS (m/z): 319 $[M+H]^+$

[0158]

[Step 2] Preparation of cyclopropyl piperidin-4-ylcarbamate

To a solution of benzyl 4-(cyclopropanecarbonylamino)piperidine-1-carboxylate obtained in Step 1 (190 mg) in ethanol (10 mL) was added 20 % palladium hydroxide (on activated carbon, 50 mg), and the medium pressure catalytic reduction was conducted. The reaction solution was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give the title compound (110 mg).
MS (m/z): 185 $[M+H]^+$

[0159]

[Step 3] Preparation of cyclopropyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using cyclopropyl piperidin-4-ylcarbamate obtained in Reference Example 21 Step 2 in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 447, 449 $[M+H]^+$

[0160]

Reference Example 22: Propan-2-yl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using propan-2-yl piperidin-4-ylcarbamate (which was prepared analogous to the method described in, for example, US 5082847) in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 449, 451 $[M+H]^+$

[0161]

Reference Example 23: Propyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Reference Example 14 Step 2,

the title compound was synthesized by using propyl piperidin-4-ylcarbamate (which was prepared analogous to the method described in, for example, US 5082847) in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 449, 451 $[M+H]^+$

[0162]

Reference Example 24: 2-Methoxyethyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

[Step 1] Preparation of 2-methoxyethyl piperidin-4-ylcarbamate

To a solution of 1-benzyloxycarbonylpiperidin-4-carboxylic acid (300 mg) in toluene (2 mL) were added TEA (556 µL), diphenylphosphoryl azide (320 µL) and 2-methoxyethanol (2 mL), and the mixture was stirred at 100 °C for 4 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give an oil (189 mg). To a solution of the resulting oil (189 mg) in methanol (10 mL) was added 5 % palladium (on activated carbon, 30 mg), and the medium pressure catalytic reduction was conducted. The reaction solution was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give the title compound (111 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.32-1.37 (2H, m), 1.94-1.97 (2H, m), 2.60-2.74 (2H, t), 3.08 (2H, d), 3.40 (3H, s), 3.57-3.59 (3H, m), 4.20-4.22 (2H, m), 4.75-4.77 (1H, m)

[0163]

[Step 2] Preparation of 2-methoxyethyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using 2-methoxyethyl piperidin-4-ylcarbamate obtained in Step 1 in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 465, 467 $[M+H]^+$

[0164]

Reference Example 25: 2,2-Difluoroethyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

[Step 1] Preparation of 2,2-difluoroethyl piperidin-4-ylcarbamate

To a solution of 2,2-difluoroethanol (100 mg) in dichloromethane (1.0 mL) were added TEA (255 µL) and triphosgene (145 mg) under ice cooling. After the mixture was stirred for 30 min, 4-amino-1-benzylpiperidine (497 µL) was added thereto and the mixture was further stirred for

30 min. To the reaction solution was added saturated aqueous sodium bicarbonate solution, and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give an oil (185 mg). To a solution of the resulting oil (185 mg) in methanol (10 mL) was added 5 % palladium (on activated carbon, 30 mg), and the medium pressure catalytic reduction was conducted. The reaction solution was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give the title compound (123 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.25-1.34 (2H, m), 1.94-1.97 (2H, m), 2.60-2.71 (2H, m), 3.04-3.08 (2H, m), 3.55-3.68 (1H, m), 4.20-4.35 (2H, m), 4.77 (1H, br), 5.78-6.08 (1H, m)

[0165]

[Step 2] Preparation of 2,2-difluoroethyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using 2,2-difluoroethyl piperidin-4-ylcarbamate obtained in Step 1 in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 471, 473 $[M+H]^+$

[0166]

Reference Example 26: 2,2,2-Trifluoroethyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Reference Example 25, the title compound was synthesized by using 2,2,2-trifluoroethanol in place of 2,2-difluoroethanol.

MS (m/z): 489, 491 $[M+H]^+$

[0167]

Reference Example 27: N-(1-{[6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide

[Step 1] Preparation of 2-methoxy-N-(4-piperidyl)acetamide

To a solution of 1-benzylpiperidin-4-amine (10 g) and TEA (15.9 mL) in dichloromethane (200 mL) was added methoxyacetyl chloride (6.3 g) dropwise under ice cooling, and the mixture was stirred for 3h. To the reaction solution was added saturated aqueous sodium bicarbonate solution, and the solution was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give an oil. A solution of the resulting oil was purified by silica gel column chromatography to give an oil (13.8 g).

To a solution of the resulting oil in ethanol (100 mL) was added 20 % palladium hydroxide (on activated carbon, 1.0 g), and the medium pressure catalytic reduction was conducted. The reaction mixture was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give the title compound (8.0 g).

MS (m/z): 173 $[M+H]^+$

[0168]

[Step 2] Preparation of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using 2-methoxy-N-(4-piperidyl)acetamide obtained in Step 1 in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 435, 437 $[M+H]^+$

[0169]

Reference Example 28: N-(1-{[6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2,2-difluoroacetamide

[Step 1] Preparation of 2,2-difluoro-N-(4-piperidyl)acetamide

To a solution of difluoroacetic acid (2.3 g) in

dichloromethane (100 mL) was added DMF (0.1 mL), oxalyl chloride (2.6 g) was added dropwise thereto under ice cooling, and the mixture was stirred for 1h. Then, 1-benzylpiperidin-4-amine (3.0 g) was added thereto, TEA (6.1 g) was added dropwise to the mixture under ice cooling, and the mixture was stirred at room temperature for 1 h. To the reaction solution was added saturated aqueous sodium bicarbonate solution, and the solution was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give an oil (500 mg). To a solution of the resulting oil in ethanol (5.0 mL) was added 20 % palladium hydroxide (on activated carbon, 300 mg), and the medium pressure catalytic reduction was conducted. The reaction mixture was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give the title compound (200 mg).

MS (m/z): 179 $[M+H]^+$

[0170]

[Step 2] Preparation of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2,2-difluoroacetamide

Analogous to the method in Reference Example 14 Step 2,

the title compound was synthesized by using 2,2-difluoro-N-(4-piperidyl)acetamide obtained in Step 1 in place of methyl piperidin-4-ylcarbamate.

^{1}H-NMR ($CDCl_3$) δ: 1.55-1.65 (4H, m), 2.04-2.15 (2H, m), 3.03-3.06 (1H, m), 3.28-3.30 (1H, m), 4.72-4.75 (1H, m) 5.91 (1H, t), 6.22-6.24 (1H, m) 7.09 (1H, d), 7.30 (1H, s), 7.90 (1H, d), 8.50 (1H, s)

[0171]

Reference Example 29: [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using piperidin-4-ol in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 364, 366 $[M+H]^+$

[0172]

Reference Example 30: (4-{[tert-Butyl(dimethyl)silyl]oxy}piperidin-1-yl)[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using 4-{[tert-butyl(dimethyl)silyl]oxy}piperidine (which was prepared analogous to the method described in, for example, WO

2004/006926) in place of methyl piperidin-4-ylcarbamate.
^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, d), 0.91 (9H, s), 1.56-1.75 (2H, m), 1.79-1.91 (2H, m), 3.40-3.50 (1H, m) 3.63-3.92 (3H, m), 4.02-4.11 (1H, m) 7.07 (1H, d), 7.26 (1H, s), 7.88 (1H, d), 8.51 (1H, s)

[0173]

Reference Example 31: N-(1-{[6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using N-(4-piperidyl)propanamide (which was prepared analogous to the method described in, for example, Bioorganic & Medicinal Chemistry Letters, 2003, 13, 2303-2306) in place of methyl piperidin-4-ylcarbamate.
MS (m/z): 419, 421 $[M+H]^+$

[0174]

Reference Example 32: [6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone

[Step 1] Preparation of N-(1-benzylpiperidin-4-yl)-3-fluoropyridin-2-amine

To a solution of 1-benzylpiperidin-4-amine (100 mg) in

DMSO (2.0 mL) were added 2,3-difluoropyridine (25 μL) and DIPEA (95 μL), and the mixture was stirred by using a microwave reactor at 130 °C for 2 h. The reaction solution was diluted with ethyl acetate, separated by adding water, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (74 mg).
MS (m/z): 286 $[M+H]^+$

[0175]

[Step 2] Preparation of 3-fluoro-N-(piperidin-4-yl)pyridin-2-amine

To a solution of N-(1-benzylpiperidin-4-yl)-3-fluoropyridin-2-amine obtained in Step 1 (970 mg) in ethanol (15 mL) were added 20 % palladium hydroxide (on activated carbon, 300 mg) and a catalytic amount of TFA, and the medium pressure catalytic reduction was conducted. The reaction solution was filtered to remove the palladium, and the mother liquid was concentrated under reduced pressure to give the title compound (770 mg).
MS (m/z): 196 $[M+H]^+$

[0176]

[Step 3] Preparation of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using 3-fluoro-N-(piperidin-4-yl)pyridin-2-amine obtained in Step 2 in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 458, 460 $[M+H]^+$

[0177]

Reference Example 33: 3-(1-{[6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-1,1-dimethylurea

[Step 1] Preparation of 3-(1-benzylpiperidin-4-yl)-1,1-dimethylurea

To a solution of 1-benzylpiperidin-4-amine (2.0 g) in dichloromethane (50 mL) was added TEA (4.4 mL), then, under ice cooling, N,N-dimethylcarbamoyl chloride (1.2 mL) was slowly added dropwise thereto, and the mixture was stirred at room temperature overnight. To the reaction mixture was added water, and the solution was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, and then, and concentrated under reduced pressure to give the title compound (2.7 g).

^{1}H-NMR ($CDCl_3$) δ: 1.43 (2H, q), 1.94 (2H, d), 2.13 (2H, t),

2.80 (2H, d), 2.88 (6H, s), 3.50 (2H, s), 3.67 (1H, m), 4.17 (1H, d), 7.22-7.32 (5H, m)

[0178]

[Step 2] Preparation of 1,1-dimethyl-3-piperidin-4-ylurea

Analogous to the method in Reference Example 21 Step 2, the title compound was synthesized by using 3-(1-benzylpiperidin-4-yl)-1,1-dimethylurea obtained in Step 1 in place of benzyl 4-(cyclopropanecarbonylamino)piperidine-1-carboxylate.

MS (m/z): 172 $[M+H]^+$

[0179]

[Step 3] Preparation of 3-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-1,1-dimethylurea

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using 1,1-dimethyl-3-piperidin-4-ylurea obtained in Step 2 in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 434, 436 $[M+H]^+$

[0180]

Reference Example 34: [6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(5-fluoropyridin-2-

yl)amino]piperidin-1-yl}methanone

[Step 1] Preparation of N-(1-benzylpiperidin-4-yl)-5-fluoropyridin-2-amine

Analogous to the method in Reference Example 32 Step 1, the title compound was synthesized by using 2,5-difluoropyridine in place of 2,3-difluoropyridine.

MS (m/z): 286 $[M+H]^+$

[0181]

[Step 2] Preparation of 5-fluoro-N-(piperidin-4-yl)pyridin-2-amine

Analogous to the method in Reference Example 32 Step 2, the title compound was synthesized by using N-(1-benzylpiperidin-4-yl)-5-fluoropyridin-2-amine obtained in Step 1 in place of N-(1-benzylpiperidin-4-yl)-3-fluoropyridin-2-amine.

^{1}H-NMR ($CDCl_3$) δ: 1.75 (2H, d), 2.24 (2H, d), 2.99 (2H, t), 3.40 (2H, d), 3.97 (1H, s), 4.28 (2H, d), 6.36 (1H, d), 7.19 (1H, t), 7.93 (1H, d)

[0182]

[Step 3] Preparation of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(5-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone

Analogous to the method in Reference Example 14 Step 2,

the title compound was synthesized by using 5-fluoro-N-(piperidin-4-yl)pyridin-2-amine obtained in Step 2 in place of methyl piperidin-4-ylcarbamate.

MS (m/z): 458, 460 $[M+H]^+$

[0183]

Reference Example 35: Methyl (1-{[6-chloro-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

[Step 1] Preparation of ethyl 6-hydroxy-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate

To a solution of methoxyacetic acid (1.0 g) and diethyl oxalate (1.24 g) in THF (10 mL) were added 60 % sodium hydride (372 mg) and ethanol (1 drop), and the mixture was stirred at room temperature for 6 h. The reaction solution was concentrated under reduced pressure to give solid. On the one hand, to a solution of pyrazolo[5,1-b][1,3]thiazole-7-carbonitrile obtained in Reference Example 1 (10 g) in methanol (300 mL) was added a solution of 28 % sodium methoxide in methanol (41 mL), and the mixture was stirred at room temperature for 1 h. Then, ammonium chloride (21.5 g) was added thereto, and the mixture was stirred at 80 °C for 2 h. The reaction solution was concentrated under reduced pressure, the resulting residue was dissolved in ethanol (5 mL), and the

solution of the above solid in ethanol (5 mL) and sodium ethoxide (576 mg) were added to the solution, and the mixture was stirred at 80 °C overnight. To the reaction mixture was added a small amount of acetic acid, the mixture was concentrated under reduced pressure, the resulting residue was diluted with ethyl acetate, and the liquid was separated by an addition of saturated aqueous sodium bicarbonate solution. The aqueous layer was further extracted with ethyl acetate, and the combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (119 mg).

MS (m/z): 321 $[M+H]^+$

[0184]

[Step 2] Preparation of 6-hydroxy-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

To a solution of ethyl 6-hydroxy-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Step 1 (115 mg) in THF (2 mL) and water (1 mL) was added lithium hydroxide monohydrate (60 mg), and the mixture was stirred at 60 °C for 6 h. To the reaction mixture was added 1 M aqueous solution of hydrochloric acid

to neutralize the mixture, which was concentrated under reduced pressure, the resulting residue was washed with water, collected on a filter, and heat-dried under reduced pressure to give the title compound (73 mg).

MS (m/z): 293 $[M+H]^+$

[0185]

[Step 3] Preparation of methyl (1-{[6-chloro-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using 6-hydroxy-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Step 2 in place of 6-hydroxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid.

MS (m/z): 451, 453 $[M+H]^+$

[0186]

Reference Example 36: Methyl (1-{[6-chloro-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

[Step 1] Preparation of 6-hydroxy-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

To a solution of 2-ethoxyethyl acetate (1 g) in THF

(10 mL) were added diethyl oxalate (1.1 g) and 60 % sodium hydride (333 mg) followed by an addition of a catalytic amount of ethanol, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the resulting residue was suspended in sodium hydroxide (762 mg) and water (10 mL).

To a solution of pyrazolo[5,1-b][1,3]thiazole-7-carbonitrile obtained in Reference Example 1 (406 mg) in methanol (10 mL) was added a solution of 28 % sodium methoxide in methanol (1.7 mL), and the mixture was stirred at room temperature for 1 h. Then, ammonium chloride (873 mg) was added thereto, and the mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure, to the resulting residue was added the above suspension, and the mixture was stirred at 100 °C for 10 h. To the reaction mixture was added conc. hydrochloric acid to make the solution acidic, the precipitated solid was collected on a filter, and dried to obtain the title compound (217 mg).

MS (m/z): 307 $[M+H]^+$

[0187]

[Step 2] Preparation of methyl (1-{[6-chloro-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Reference Example 14 Step 2, the title compound was synthesized by using 6-hydroxy-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Step 1 in place of 6-hydroxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid .

MS (m/z): 465, 467 $[M+H]^+$

[0188]

Reference Example 37: 6-{[(2S)-1-(Difluoromethoxy)propan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

[Step 1] Preparation of methyl 6-{[(2S)-1-(difluoromethoxy)propan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate

To a solution of methyl 6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Reference Example 3 (30 mg) in DMF (0.5 mL) was added (2S)-1-(difluoromethoxy)propan-2-amine hydrochloride obtained in Reference Example 6 (21 mg) and DIPEA (0.1 mL), and the mixture was stirred at 100 °C for 3 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (22 mg).

MS (m/z): 384 $[M+H]^+$

[0189]

[Step 2] Preparation of 6-{[(2S)-1-(difluoromethoxy)propan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

To a solution of methyl 6-{[(2S)-1-(difluoromethoxy)propan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-carboxylate obtained in Step 1 (15 mg) in THF (3 mL) and water (1 mL) was added lithium hydroxide monohydrate (5 mg), and the mixture was stirred at 50 °C for 2 h.. To the reaction mixture was added 1 M aqueous solution of hydrochloric acid to make the solution acidic, the aqueous layer was extracted with a mixed solvent of chloroform and methanol, the organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (17 mg).

MS (m/z): 370 $[M+H]^+$

[0190]

Reference Example 38: 6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

[Step 1] Preparation of methyl 6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-

yl)pyrimidine-4-carboxylate

To a solution of methyl 6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Reference Example 3 (50 mg) in DMF (2 mL) were added DIPEA (88 µL) and (1S)-1-cyclopropylethanamine (16 mg), and the mixture was stirred at 80 °C for 3 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (40 mg).

MS (m/z): 344 $[M+H]^+$

[0191]

[Step 2] Preparation of 6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

To a solution of methyl 6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Step 1 (40 mg) in THF (9 mL) and water (3 mL) was added lithium hydroxide monohydrate (10 mg), and the mixture was stirred at room temperature for 1 h. To the reaction mixture was added 1 M aqueous solution of hydrochloric acid to make the solution acidic, THF was distilled off under reduced pressure, and the aqueous layer was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title

compound (36 mg).

MS (m/z): 330 $[M+H]^+$

[0192]

Reference Example 39: 6-{[(1R)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

Analogous to the method in Reference Example 38 Steps 1 and 2, the title compound was synthesized by using (1R)-1-cyclopropylethanamine in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 330 $[M+H]^+$

[0193]

Reference Example 40: 6-{[(2S)-3,3-Dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

Analogous to the method in Reference Example 38 Steps 1 and 2, the title compound was synthesized by using (2S)-3,3-dimethylbutan-2-amine in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 346 $[M+H]^+$

[0194]

Reference Example 41: 6-{[(2R)-3,3-Dimethylbutan-2-

yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

Analogous to the method in Reference Example 38 Steps 1 and 2, the title compound was synthesized by using (2R)-3,3-dimethylbutan-2-amine in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 346 $[M+H]^+$

[0195]

Reference Example 42: 6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

Analogous to the method in Reference Example 38 Steps 1 and 2, the title compound was synthesized by using (1S,2S)-2-(difluoromethoxy)cyclopentanamine hydrochloride obtained in Reference Example 7 in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 396 $[M+H]^+$

[0196]

Reference Example 43: Methyl 6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate

To a solution of methyl 6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-

yl)pyrimidine-4-carboxylate obtained in Reference Example 38 Step 1 (820 mg) in DMF (8.0 mL) was added 60 % sodium hydride (115 mg) at room temperature, and the mixture was stirred for 3 min. Then, iodomethane (1.4 g) was added thereto and the mixture was stirred for 5 min. Further, an additional 60 % sodium hydride (11 mg) was added thereto and the mixture was stirred for 5 min. The reaction solution was diluted with chloroform, separated by adding water, the aqueous layer was further extracted with chloroform, and the combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (665 mg).

MS (m/z): 358 $[M+H]^+$

[0197]

Reference Example 44: 6-{[(1R)-1-(4-methoxyphenyl)ethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

Analogous to the method in Reference Example 38 Steps 1 and 2, the title compound was synthesized by using (1R)-1-(4-methoxyphenyl)ethanamine in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 396 $[M+H]^+$

[0198]

Reference Example 45: 6-{[(1S,2S)-2-(Difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

[Step 1] Preparation of methyl 6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate

To a solution of benzyl [(1S,2S)-2-(difluoromethoxy)cyclopentyl]carbamate obtained in Reference Example 7 Step 2 (710 mg) in DMF (5 mL) was added 60 % sodium hydride (149 mg) in portions at room temperature, and the resulting mixture was stirred at 10 min. Then, iodomethane (530 mg) was added thereto, and the mixture was stirred for 2 h. The reaction mixture was diluted with ethyl acetate, separated by adding water, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give an oil (338 mg). To a solution of the resulting oil (300 mg) in ethanol (6 mL) was added 20 % palladium hydroxide (on activated carbon, 100 mg), and the medium pressure catalytic reduction was conducted. To the mixture was added 4 M hydrogen chloride-ethyl acetate, the

reaction solution was filtered to remove the palladium, the mother liquid was concentrated under reduced pressure to give a solid (271 mg). To a solution of the obtained solid (75 mg) and methyl 6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Reference Example 3 (100 mg) in DMF (2 mL) was added DIPEA (0.18 mL), and the mixture was stirred at 100 °C for 3 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (102 mg).

MS (m/z): 424 $[M+H]^+$

[0199]

[Step 2] Preparation of 6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

Analogous to the method in Reference Example 38 Step 2, the title compound was synthesized by using methyl 6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Step 1 in place of methyl 6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate.

MS (m/z): 410 $[M+H]^+$

[0200]

Reference Example 46: 6-{[(1S,2S)-2-methoxycyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

[Step 1] Preparation of methyl 6-{[(1S,2S)-2-methoxycyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate

To a solution of tert-butyl N-[(1S,2S)-2-hydroxycyclopentyl]carbamate (4.0 g) in DMF (20 mL) was added 60 % sodium hydride (870 mg) in portions under ice cooling, and the mixture was stirred at room temperature for 10 min. Then, iodomethane (3.1 g) was added thereto under ice cooling, and the mixture was stirred at room temperature. The reaction mixture was diluted with ethyl acetate, separated by adding water, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give a solid 1 (2.3 g). To a solution of the obtained solid 1 in dichloromethane (10 mL) was added 4 M hydrogen chloride-ethyl acetate solution (5.3 mL), and the mixture was stirred at room temperature for 4 h. The solvent was concentrated under reduced pressure to give a solid 2 (1.5 g). To a solution of the obtained

solid 2 (93 mg) and methyl 6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Reference Example 3 (150 mg) in DMF (2.0 mL) was added DIPEA (0.26 mL), and the mixture was stirred at 100 °C for 3 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (112 mg).
MS (m/z): 374 $[M+H]^+$

[0201]

[Step 2] Preparation of 6-{[(1S,2S)-2-methoxycyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

Analogous to the method in Reference Example 38 Step 2, the title compound was synthesized by using methyl 6-{[(1S,2S)-2-methoxycyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Step 1 in place of methyl 6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate.
MS (m/z): 360 $[M+H]^+$

[0202]

Reference Example 47: 6-{[(2S)-3,3-Dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

[Step 1] Preparation of methyl 6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate

To a solution of methyl 6-chloro-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-carboxylate obtained in Reference Example 5 (50 mg) in NMP (1 mL) were added (2S)-3,3-dimethylbutan-2-amine (33 mg) and DIPEA (56 µL), and the mixture was stirred at 110 °C for 2 h 30 min. The mixture was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, the aqueous layer was further extracted with ethyl acetate, and the combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (39 mg).
MS (m/z): 374 $[M+H]^+$

[0203]

[Step 2] Preparation of 6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

To a solution of methyl 6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Step 1 (35 mg) in THF (5.0 mL) and water (2.0 mL) was added lithium hydroxide

monohydrate (12 mg), and the mixture was stirred at 50 °C for 1 h. To the reaction mixture was added 1 M aqueous solution of hydrochloric acid to make the solution acidic, the aqueous layer was extracted with a mixed solvent of chloroform and methanol. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (35 mg).

MS (m/z): 360 $[M+H]^+$

[0204]

Reference Example 48: 6-{[(1S)-1-Cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

Analogous to the method in Reference Example 47 Steps 1 and 2, the title compound was synthesized by using (1S)-1-cyclopropylethanamine in place of (2S)-3,3-dimethylbutan-2-amine.

MS (m/z): 344 $[M+H]^+$

[0205]

Reference Example 49: 6-[(2,2-Dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid

Analogous to the method in Reference Example 38 Steps 1 and 2, the title compound was synthesized by using 2,2-

dimethylpropan-1-amine in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 332 $[M+H]^+$

[0206]

Reference Example 50: 1-cyclopropyl-3-piperidin-4-ylurea hydrochloride

To a solution of cyclopropanecarboxylic acid (300 mg) in toluene (3 mL) were added TEA (0.5 mL) and diphenylphosphoryl azide (1.1 g), and the mixture was stirred at 80 °C for 3 h. Then, tert-butyl 4-aminopiperidine-1-carboxylate (600 mg) was added thereto at room temperature, and the mixture was stirred for 1 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give a solid (234 mg). To a solution of the obtained solid (230 mg) in dichloromethane (5 mL) was added 4 M hydrogen chloride-ethyl acetate solution (0.6 mL), and the mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure to give the title compound (200 mg).

MS (m/z): 184 $[M-Cl]^+$

[0207]

Reference Example 51: 1-Fluoro-2-methylpropan-2-yl

piperidin-4-ylcarbamate

To a solution of 1-benzylpiperidin-4-amine (4.0 g) and 1-{[(1-fluoro-2-methylpropan-2-yl)oxy]carbonyl}-3-methyl-1H-imidazole-3-ium iodide (7.6 g) (which was prepared analogous to the method described in, for example, Bioorganic Medicinal Chemistry, 2011, 19, 1580-1593) in acetonitrile (20 mL) was added TEA (5.9 mL), and the mixture was stirred at room temperature for 1 h. To the reaction mixture was added water, and the solution was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give a solid (2.0 g). To a solution of the obtained solid (2.0 g) in ethanol (20 mL) was added 20 % palladium hydroxide (on activated carbon, 1.0 g), and the medium pressure catalytic reduction was conducted. The reaction solution was filtered to remove the palladium, the mother liquid was concentrated under reduced pressure, and the resulting residue was washed with ethyl acetate to give the tile compound (306 mg).
MS (m/z): 219 $[M+H]^+$

[0208]

Reference Example 52: 2-(Dimethylamino)ethyl piperidin-4-ylcarbamate

Analogous to the method in Reference Example 25 Step 1, the title compound was synthesized by using 2-dimethylaminoethanol in place of 2,2-difluoroethanol.
^{1}H-NMR ($CDCl_3$) δ: 1.21-1.35 (2H, m), 1.90-2.00 (2H, m), 2.28 (6H, s), 2.51-2.59 (2H, m), 2.62-2.70 (2H, m), 3.00-3.10 (2H, m), 3.52-3.64 (1H, m), 4.14 (2H, t), 4.74 (1H, br)

[0209]

Example 1: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide hydrochloride

[Step 1] Preparation of N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of 6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 38 (15 mg) in DMF (1.0 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (11 mg), DIPEA (24 μL) and HATU (26 mg), and the mixture was stirred at room temperature for 1 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (9 mg).

MS (m/z): 480 $[M+H]^+$

[0210]

[Step 2] Preparation of N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide hydrochloride

To a solution of N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide obtained in Step 1 (540 mg) in dichloromethane was added 4 M hydrogen chloride-ethyl acetate solution (0.5 mL). The reaction solution was concentrated under reduced pressure to give the title compound (580 mg).

MS (m/z): 480 $[M-Cl]^+$

Specific rotation $[\alpha]_D^{25}=-45.2°$ (c=1.00, DMSO)

[0211]

Example 2: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide

Analogous to the method in Example 1 Step 1, the title compound was synthesized by using N-(4-piperidyl)acetamide in place of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 454 $[M+H]^+$

[0212]

Example 3: N-(1-{[6-{[(2S)-3,3-Dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of 6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 40 (15 mg) in DMF (1.0 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (11 mg), DIPEA (23 µL) and HATU (25 mg), and the mixture was stirred at room temperature for 1 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (7 mg).
MS (m/z): 496 $[M+H]^+$

[0213]

Example 4: N-(1-{[6-{[(2S)-3,3-Dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide

Analogous to the method in Example 3, the title compound was synthesized by using N-(4-piperidyl)acetamide in place of N-(piperidin-4-yl)cyclopropanecarboxamide.
MS (m/z): 470 $[M+H]^+$

[0214]

Example 5: N-(1-{[6-{[(1S,2S)-2-(Difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of 6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 45 (15 mg) in DMF (1.0 mL) was added N-(piperidin-4-yl)cyclopropanecarboxamide (9.0 mg), DIPEA (19 μL) and HATU (21 mg), and the mixture was stirred at room temperature for 3 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (16 mg).

MS (m/z): 560 $[M+H]^+$

[0215]

Example 6: N-(1-{[6-{[(2S)-3,3-Dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide

To a solution of 6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 47 (15 mg) and N-(4-piperidyl)acetamide (9.0 mg) in DMF (1.0 mL) was added DIPEA (14 μL) and HATU (24 mg), and

the mixture was stirred at room temperature for 1 h 30 min. The reaction mixture was purified by silica gel column chromatography to give the title compound (15 mg).
MS (m/z): 484 $[M+H]^-$

[0216]

Example 7: N-(1-{[6-{[(2S)-3,3-Dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 6, the title compound was synthesized by using N-(piperidin-4-yl)cyclopropanecarboxamide in place of N-(4-piperidyl)acetamide.
MS (m/z): 510 $[M+H]^+$

[0217]

Example 8: N-[1-({6-[({1-[(Difluoromethoxy)methyl]cyclopropyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

To a solution of methyl 6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Reference Example 3 (200 mg) in DMF (1.5 mL) were added {1-[(difluoromethoxy)methyl]cyclopropyl}methanamine obtained in Reference Example 8 (113 mg) and DIPEA (236 μL), and the

mixture was stirred at 80 °C for 1 h 30 min. To the reaction solution was added water, the solution was extracted with ethyl acetate, and the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give a solid 1 (233 mg). To a solution of the obtained solid 1 (210 mg) in THF (4.0 mL) and water (1.0 mL) was added lithium hydroxide monohydrate (32 mg), and the mixture was stirred at 40 °C for 20 min. The reaction solution was neutralized with 1 M aqueous solution of hydrochloric acid, and concentrated under reduced pressure to give a solid 2 (246 mg). To a solution of the obtained solid 2 (40 mg) in DMF (0.5 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (26 mg), DIPEA (35 μL) and HATU (58 mg), and the mixture was stirred at room temperature overnight. To the reaction solution was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (25 mg).

MS (m/z): 546 $[M+H]^+$

[0218]

Example 9: N-[1-({6-[({1-[(Difluoromethoxy)methyl]cyclobutyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

Analogous to the method in Example 8, the title compound was synthesized by using {1-[(difluoromethoxy)methyl]cyclobutyl}methanamine obtained in Reference Example 9 in place of {1-[(difluoromethoxy)methyl]cyclopropyl}methanamine.

MS (m/z): 560 $[M+H]^+$

[0219]

Example 10: N-[1-({6-[({1-[(Difluoromethoxy)methyl]cyclopentyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

Analogous to the method in Example 8, the title compound was synthesized by using {1-[(difluoromethoxy)methyl]cyclopentyl}methanamine obtained in Reference Example 10 in place of {1-[(difluoromethoxy)methyl]cyclopropyl}methanamine.

MS (m/z): 574 $[M+H]^+$

[0220]

Example 11: N-[1-({6-[({4-[(Difluoromethoxy)methyl]tetrahydro-2H-pyran-4-yl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

Analogous to the method in Example 8, the title compound was synthesized by using {4-[(difluoromethoxy)methyl]tetrahydro-2H-pyran-4-yl}methanamine obtained in Reference Example 11 in place of {1-[(difluoromethoxy)methyl]cyclopropyl}methanamine.
MS (m/z): 590 $[M+H]^+$

[0221]

Example 12: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of 6-{[(1S)-1-cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 48 (20 mg) in DMF (1 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (15 mg), DIPEA (20 μL) and HATU (33 mg), and the mixture was stirred at room temperature for 1 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (21 mg).
MS (m/z): 494 $[M+H]^+$

[0222]

Example 13: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide

Analogous to the method in Example 12, the title compound was synthesized by using N-(4-piperidyl)acetamide in place of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 468 $[M+H]^+$

[0223]

Example 14: N-(1-{[6-{[(1S,2S)-2-(Difluoromethoxy)cyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of 6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 42 (20 mg) in DMF (1 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (13 mg), DIPEA (26 µL) and HATU (29 mg), and the mixture was stirred at room temperature for 1 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (7 mg).

MS (m/z): 546 $[M+H]^+$

[0224]

Example 15: N-[1-({6-[(2,2-Dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

To a solution of methyl 6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Reference Example 3 (30 mg) in DMF (0.1 mL) were added 2,2-dimethylpropan-1-amine (9.0 mg) and DIPEA (50 µL), and the mixture was stirred at 100 °C for 3 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give a solid 1 (28 mg). To a solution of the obtained solid 1 (28 mg) in dioxane (5.0 mL) and water (1.0 mL) was added lithium hydroxide monohydrate (7 mg), and the mixture was stirred at 50 °C for 1 h. The mixture was neutralized with 2 M hydrochloric acid aqueous solution, and the reaction solution was concentrated under reduced pressure to give a solid 2. To a solution of the obtained solid 2 in DMF (1.5 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide, DIPEA (0.2 mL) and HATU (62 mg), and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (27

mg).

MS (m/z): 482 $[M+H]^+$

[0225]

Example 16: N-(1-{[6-{[(2R)-3,3-Dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Under argon atmosphere, N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide obtained in Reference Example 15 (550 mg) in tert-butanol (20 mL) was added TEA (534 µL) and (2R)-3,3-dimethylbutan-2-amine (258 mg), and the mixture was stirred at 90 °C overnight. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (570 mg).

MS (m/z): 496 $[M+H]^+$

Specific rotation $[\alpha]_D^{25}$=+14.0°(c=1.00,DMSO)

[0226]

Example 17: N-(1-{[6-{[(2S)-1-(Difluoromethoxy)propan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of 6-{[(2S)-1-(difluoromethoxy)propan-2-

yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 37 (20 mg) in DMF (0.5 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (11 mg), DIPEA (10 µL) and HATU (40 mg), and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (13 mg).

MS (m/z): 520 $[M+H]^+$

[0227]

Example 18: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2,2-difluoroacetamide

Analogous to the method in Example 12, the title compound was synthesized by using 2,2-difluoro-N-(4-piperidyl)acetamide obtained in Example 28 Step 1 in place of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 504 $[M+H]^+$

[0228]

Example 19: N-(1-{[6-{[(1S,2S)-2-Methoxycyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of 6-{[(1S,2S)-2-methoxycyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 46 (20 mg) in DMF (1 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (14 mg), DIPEA (29 µL) and HATU (32 mg), and the mixture was stirred at room temperature for 30 min. The reaction mixture was purified by silica gel column chromatography to give the title compound (13 mg).

MS (m/z): 510 $[M+H]^+$

[0229]

Example 20: [6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone hydrochloride

To a solution of 6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 38 (420 mg) in DMF (5 mL) were added piperidin-4-ol (194 mg), DIPEA (662 µL) and HATU (727 mg), and the mixture was stirred at room temperature for 1 h. The reaction mixture was purified by silica gel column chromatography to give a solid (530 mg). To a solution of the obtained solid in ethyl acetate was added 4 M hydrogen chloride-ethyl acetate solution (0.6 mL). The reaction solution was concentrated under reduced

pressure to give the title compound (560 mg).

MS (m/z): 413 $[M-Cl]^+$

Elemental analysis value (for $C_{19}H_{24}N_6O_2S \cdot HCl + 0.3\ H_2O + 0.2\ CH_3CO_2C_2H_5$)

Calculated value (%) C: 52.93, H: 5.81, N: 17.81

Found value (%) C: 52.68, H: 5.78, N: 17.78

[0230]

Example 21: 1-Fluoro-2-methylpropan-2-yl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate hydrochloride

Analogous to the method in Example 20, the title compound was synthesized by using 1-fluoro-2-methylpropan-2-yl piperidin-4-ylcarbamate obtained in Reference Example 51 in place of piperidin-4-ol.

MS (m/z): 530 $[M-Cl]^+$

[0231]

Example 22: Methyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 3, the title compound was synthesized by using Reference Example 14 obtained in Step 1 methyl piperidin-4-ylcarbamate in place

of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 486 $[M+H]^+$

[0232]

Example 23: [6-{[(2S)-3,3-Dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone

Analogous to the method in Example 3, the title compound was synthesized by using piperidin-4-ol in place of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 429 $[M+H]^+$

[0233]

Example 24: Methyl (1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate hydrochloride

[Step 1] Preparation of methyl (1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Under argon atmosphere, to a solution of methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 14 (20 mg) in DMF (1 mL) was added DIPEA (16 µL), (2R)-3-methylbutan-2-amine (6 mg), and the mixture was stirred at 100 °C for 3 h 30 min. The reaction solution

was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (19 mg).

MS (m/z): 472 $[M+H]^+$

[Step 2] Preparation of methyl (1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate hydrochloride

To a solution of methyl (1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Step 1 (56 mg) in ethyl acetate was added 4 M hydrogen chloride-ethyl acetate solution (0.1 mL). The reaction solution was concentrated under reduced pressure, and the resulting residue was washed with diethyl ether to give the title compound (50 mg).

MS (m/z): 472 $[M-Cl]^+$

Elemental analysis value (for $C_{22}H_{29}N_7O_3S \cdot HCl + 1.0\ H_2O$)

Calculated value (%) C: 50.23, H: 6.13, N: 18.64

Found value (%) C: 50.47, H: 6.08, N: 18.52

[0234]

Example 25: Methyl (1-{[6-{[(2S)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate hydrochloride

Analogous to the method in Example 24 Steps 1 and 2, the title compound was synthesized by using (2S)-3-methylbutan-2-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 472 $[M-Cl]^+$

Elemental analysis value (for $C_{22}H_{29}N_7O_3S \cdot HCl + H_2O$)

Calculated value (%) C: 50.23, H: 6.13, N: 18.64

Found value (%) C: 50.50, H: 6.10, N: 18.27

[0235]

Example 26: Methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using (1S)-1-cyclopropylethanamine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 470 $[M+H]^+$

Specific rotation $[\alpha]_D^{25}$=-53.0°(c=1.00,DMSO)

Example 27: Methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate hydrochloride

To a solution of methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Example 26 (2.26 g) in ethyl acetate (100 mL) was added 4 M hydrogen chloride-ethyl acetate solution (2.4 mL). The reaction solution was concentrated under reduced pressure to give the title compound (2.35 g).

MS (m/z): 470 $[M-Cl]^+$

Elemental analysis value (for $C_{22}H_{27}N_7O_3S \cdot HCl + H_2O$)

Calculated value (%) C: 50.42, H: 5.77, N: 18.71

Found value (%) C: 50.53, H: 5.66, N: 18.97

[0236]

Example 28: Ethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 1 Step 1, the title compound was synthesized by using ethyl piperidin-4-ylcarbamate (which was prepared analogous to the method described in, for example, US 1990/4918073) in place of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 484 $[M+H]^+$

Specific rotation $[\alpha]_D^{25}$=-44.2°(c=1.00,DMSO)

[0237]

Example 29: Propan-2-yl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of propan-2-yl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 22 (200 mg) in DMF (3 mL) were added DIPEA (0.3 mL) and (2R)-3,3-dimethylbutan-2-amine (90 mg), and the mixture was stirred at 120 °C for 4 h in a sealed tube. The reaction solution was diluted with ethyl acetate, separated by using saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (160 mg).

MS (m/z): 514 $[M+H]^+$

[0238]

Example 30: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide

[Step 1] Preparation of tert-butyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 1 Step 1, the title compound was synthesized by using tert-butyl N-(4-piperidyl)carbamate in place of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 512 $[M+H]^+$

[Step 2] Preparation of (4-aminopiperidin-1-yl)[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone

To a solution of tert-butyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Step 1 (75 mg) in dichloromethane (2 mL) was added TFA (0.5 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (65 mg).

MS (m/z): 412 $[M+H]^+$

[Step 3] Preparation of N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide

To a solution of (4-aminopiperidin-1-yl)[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone obtained in Step 2 (20 mg) in dichloromethane (1 mL) was added DIPEA (25 µL), benzoyl chloride (10 mg), and the mixture was stirred at room temperature for 30 min. The reaction mixture was purified by silica gel column chromatography to give the title compound (18 mg).

MS (m/z): 516 $[M+H]^+$

[0239]

Example 31: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)pyridine-3-carboxamide

Analogous to the method in Example 30 Step 3, the title compound was synthesized by using pyridine-3-carbonyl chloride hydrochloride in place of benzoyl chloride.

MS (m/z): 517 $[M+H]^+$

[0240]

Example 32: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)thiophene-2-carboxamide

Analogous to the method in Example 30 Step 3, the title compound was synthesized by using thiophene-2-carbonyl chloride in place of benzoyl chloride.

MS (m/z): 522 $[M+H]^+$

[0241]

Example 33: N-(1-{[6-{[(1S)-1-Cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide hydrochloride

[Step 1] Preparation of N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of methyl 6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Reference Example 43 (25 mg) in THF (3 mL) and water (1 mL) was added lithium hydroxide monohydrate (9 mg), and the mixture was stirred at room temperature for 30 min. The reaction solution was concentrated under reduced pressure, and to a solution of the obtained solid in DMF (2 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (18 mg), DIPEA (74 μL) and HATU (40 mg), and the mixture was stirred

at room temperature for 1 h. The reaction solution was diluted with chloroform, separated by adding water, and the aqueous layer was further extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (30 mg).

MS (m/z): 494 $[M+H]^+$

[Step 2] Preparation of N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide hydrochloride

Analogous to the method in Example 27 , the title compound was synthesized by using N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide obtained in Step 1.

MS (m/z): 494 $[M-Cl]^+$

Specific rotation $[\alpha]_D^{25}=-35.7°$ (c=0.42, DMSO)

[0242]

Example 34: 1-Cyclopropyl-3-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)urea

Analogous to the method in Example 1 Step 1, the title compound was synthesized by using 1-cyclopropyl-3-piperidin-4-ylurea hydrochloride obtained in Reference Example 50 in place of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 495 $[M+H]^+$

[0243]

Example 35: [6-{[(1S)-1-Cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyrimidin-2-ylamino)piperidin-1-yl]methanone

To a solution of methyl 6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Reference Example 43 (665 mg) in THF (10 mL) and water (5 mL) was added lithium hydroxide monohydrate (234 mg), and the mixture was stirred at room temperature for 30 min. The reaction solution was concentrated under reduced pressure, to the resulting residue 1 M aqueous solution of hydrochloric acid to make the solution acidic, and the aqueous layer was extracted with a mixed solvent of chloroform and methanol. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a solid (600 mg). To a solution of the obtained solid (15 mg) in DMF (1 mL) were added N-(4-

piperidyl)pyrimidin-2-amine (which was prepared analogous to the method described in, for example, WO 2005/105779) (12 mg), DIPEA (15 μL), HATU (25 mg), and the mixture was stirred at room temperature for 1 h 30 min. The reaction mixture was purified by silica gel column chromatography to give the title compound (14 mg).

MS (m/z): 504 $[M+H]^+$

[0244]

Example 36: N-(1-{[6-(tert-Butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

[Step 1] Preparation of methyl 6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate

To a solution of methyl 6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Reference Example 3 (30 mg) in DMF (0.5 mL) were added DIPEA (50 μL) and tert-butylamine (7 mg), and the mixture was stirred at 100 °C for 3 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (15 mg).

MS (m/z): 332 $[M+H]^+$

[Step 2] Preparation of N-(1-{[6-(tert-butylamino)-2-

(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of methyl 6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Step 1 (15 mg) in THF (5 mL) and water (1 mL) was added lithium hydroxide monohydrate (6 mg), and the mixture was stirred at 40 °C for 1 h. The mixture was neutralized with 2 M hydrochloric acid aqueous solution, and the reaction solution was concentrated under reduced pressure to give a solid. To a solution of the obtained solid in DMF (0.5 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (11 mg), DIPEA (16 µL) and HATU (26 mg), and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (8 mg).

MS (m/z): 468 $[M+H]^+$

[0245]

Example 37: N-[1-({6-[(1-Methylcyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

Analogous to the method in Example 36 Steps 1 and 2, the title compound was synthesized by using 1-

methylcyclopropanamine hydrochloride in place of tert-butylamine.

MS (m/z): 466 $[M+H]^+$

[0246]

Example 38: N-[1-({6-[(1-Methoxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

Analogous to the method in Example 36 Steps 1 and 2, the title compound was synthesized by using 1-methoxy-2-methylpropan-2-amine hydrochloride (which was prepared analogous to the method described in, for example, WO 2011/087837) in place of tert-butylamine.

MS (m/z): 498 $[M+H]^+$

[0247]

Example 39: Methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using (2R)-3,3-dimethylbutan-2-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 486 $[M+H]^+$

[0248]

Example 40: Ethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of 6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 41 (30 mg) in DMF (1 mL) were added ethyl piperidin-4-ylcarbamate (which was prepared analogous to the method described in US 1990/4918073) (19 mg), DIPEA (34 mg) and HATU (50 mg), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (41 mg).
MS (m/z): 500 $[M+H]^+$

[0249]

Example 41: Propan-2-yl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 29, the title compound was synthesized by using (1S)-1-cyclopropylethanamine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 498 $[M+H]^+$

Specific rotation $[\alpha]_D^{25}$=-35.4°(c=0.74,DMSO)

[0250]

Example 42: N-(1-{[6-{[(1S)-1-Cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide

[Step 1] Preparation of tert-butyl (1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 35, the title compound was synthesized by using tert-butyl N-(4-piperidyl)carbamate in place of N-(4-piperidyl)pyrimidin-2-amine.

MS (m/z): 526 $[M+H]^+$

[Step 2] Preparation of (4-aminopiperidin-1-yl)[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone

To a solution of tert-butyl (1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Step 1 (150 mg) in dichloromethane (2 mL) was added TFA (1 mL), and the mixture was stirred at room temperature for 30 min. The reaction mixture was purified by silica gel column chromatography to give the title compound (117 mg).

MS (m/z): 426 $[M+H]^+$

[0251]

[Step 3] Preparation of N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide

To a solution of (4-aminopiperidin-1-yl)[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone obtained in Step 2 (20 mg) in dichloromethane (1 mL) was added DIPEA (24 μL), benzoyl chloride (10 mg), and the mixture was stirred at room temperature for 30 min. The reaction mixture was purified by silica gel column chromatography to give the title compound (13 mg).

MS (m/z): 530 $[M+H]^+$

[0252]

Example 43: N-(1-{[6-(Cyclopropylmethoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide obtained in Reference Example 15 (20 mg) and cyclopropylmethanol (33 mg) in THF (3.0 mL) was added 60 % sodium hydride (2 mg) under ice cooling, and the mixture was stirred at 70 °C for 1 h. The reaction solution was diluted with ethyl acetate, separated by adding water, the aqueous layer was further extracted with ethyl acetate. The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (15 mg).

MS (m/z): 467 $[M+H]^+$

[0253]

Example 44: N-[1-({6-[(3,3-Dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

Analogous to the method in Example 43, the title compound was synthesized by using 3,3-dimethylbutan-2-ol in

place of cyclopropylmethanol.

MS (m/z): 497 $[M+H]^+$

[0254]

Example 45: N-(1-{[6-(Cyclobutyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 43, the title compound was synthesized by using cyclobutanol in place of cyclopropylmethanol.

MS (m/z): 467 $[M+H]^+$

[0255]

Example 46: N-(1-{[6-{[(1R)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using (1R)-1-cyclopropylethanamine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 480 $[M+H]^+$

[0256]

Example 47: N-(1-{[6-{[(1R)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide hydrochloride

To a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide obtained in Reference Example 15 (50 mg) in DMF (1 mL) were added DIPEA (60 µL) and (1R)-1-cyclopropylethanamine (12 mg), and the mixture was stirred at 70 °C for 1 h 40 min. Then, (1R)-1-cyclopropylethanamine (11 mg) was added thereto, and the mixture was stirred at 70 °C for 4 h. The reaction solution was diluted with ethyl acetate, separated by adding water, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give a solid (50 mg). To a solution of the obtained solid in ethyl acetate was added 4 M hydrogen chloride-ethyl acetate solution (52 µL). The reaction solution was concentrated under reduced pressure, and the resulting residue was washed with diethyl ether to give the title compound (35 mg).

MS (m/z): 481 $[M-Cl]^+$

[0257]

Example 48: N-[1-({6-[(1-Hydroxy-2-methylpropan-2-

yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

To a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide obtained in Reference Example 15 (20 mg) in NMP (1 mL) were added DIPEA (16 µL) and 2-amino-2-methylpropan-1-ol (6 mg), and the mixture was stirred at 100 °C for 2 h. An additional 2-amino-2-methylpropan-1-ol (6 mg) was added thereto, and the mixture was stirred at 110 °C for 2 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (8 mg).

MS (m/z): 484 $[M+H]^+$

[0258]

Example 49: [6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,2-oxazol-3-ylamino)piperidin-1-yl]methanone

Under argon atmosphere, tert-butyl 4-oxopiperidine-1-carboxylate (250 mg) and isoxazole-3-amine (106 mg) in methanol (5 mL) were added acetic acid (75 mg) and 2-picoline borane complex (134 mg), and the mixture was stirred at room temperature for 3 h. To the reaction mixture was added saturated aqueous sodium bicarbonate solution, and the solution was extracted with ethyl acetate.

The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give an oil (109 mg). The resulting oil was dissolved in 2M hydrogen chloride-methanol solution (5 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the resulting residue was washed with diethyl ether, and dried to give a solid (90 mg). To a solution of the obtained solid (9 mg) and 6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 38 (10 mg) in DMF (1 mL) were added DIPEA (11 μL) and HATU (17 mg), and the mixture was stirred at room temperature for 1 h 30 min. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (14 mg).

MS (m/z): 479 $[M+H]^+$

[0259]

Example 50: [6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone

Analogous to the method in Example 49, the title

compound was synthesized by using thiazole-2-amine in place of isoxazole-3-amine.

MS (m/z): 495 $[M+H]^+$

[0260]

Example 51: [6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-methyl-1,2-oxazol-5-yl)amino]piperidin-1-yl}methanone

Analogous to the method in Example 49, the title compound was synthesized by using 3-methylisoxazole-5-amine in place of isoxazole-3-amine.

MS (m/z): 493 $[M+H]^+$

[0261]

Example 52: N-(1-{[6-{[(1R)-1-(4-Methoxyphenyl)ethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of 6-{[(1R)-1-(4-methoxyphenyl)ethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 44 (20 mg) in DMF (1 mL) were added N-(piperidin-4-yl)cyclopropanecarboxamide (12 mg), DIPEA (26 µL) and HATU (29 mg), and the mixture was stirred at room temperature for 1 h. The reaction mixture was purified by silica gel

column chromatography to give the title compound (16 mg).
MS (m/z): 546 $[M+H]^+$

[0262]

Example 53: Methyl (1-{[6-{[(1R)-1-(4-methoxyphenyl)ethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 52, the title compound was synthesized by using Reference Example 14obtained in Step 1 methyl piperidin-4-ylcarbamate in place of N-(piperidin-4-yl)cyclopropanecarboxamide.
MS (m/z): 536 $[M+H]^+$

[0263]

Example 54: N-(1-{[6-{[(1R)-1-(4-Methoxyphenyl)ethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide

Analogous to the method in Example 52, the title compound was synthesized by using N-(4-piperidyl)benzamide in place of N-(piperidin-4-yl)cyclopropanecarboxamide.
MS (m/z): 582 $[M+H]^+$

[0264]

Example 55: N-(1-{[6-{[(2S)-1-Hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 48, the title compound was synthesized by using (2S)-2-amino-3,3-dimethylbutan-1-ol in place of 2-amino-2-methylpropan-1-ol.

MS (m/z): 512 $[M+H]^+$

[0265]

Example 56: (4-Hydroxypiperidin-1-yl)[6-{[(1R)-1-(4-methoxyphenyl)ethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone

Analogous to the method in Example 52, the title compound was synthesized by using piperidin-4-ol in place of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 479 $[M+H]^+$

[0266]

Example 57: 1-Fluoro-2-methylpropan-2-yl (1-{[6-{[(1R)-1-(4-methoxyphenyl)ethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 52, the title compound was synthesized by using 1-fluoro-2-methylpropan-2-yl piperidin-4-ylcarbamate obtained in Reference Example 51 in place of N-(piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 596 $[M+H]^+$

[0267]

Example 58: [6-(tert-Butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone

To a solution of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone obtained in Reference Example 29 (2.2 g) in tert-butanol (10 mL) was added tert-butylamine (1.3 g), and the mixture was stirred at 130 °C for 10 h in a sealed tube. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (2.1 g).

MS (m/z): 401 $[M+H]^+$

[0268]

Example 59: Methyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using tert-butylamine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 458 $[M+H]^+$

[0269]

Example 60: Propan-2-yl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 29, the title compound was synthesized by using tert-butylamine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 486 $[M+H]^+$

[0270]

Example 61: Methyl [1-({6-[(1-hydroxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using 2-amino-2-methylpropan-1-ol in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 474 $[M+H]^+$

[0271]

Example 62: [6-{[(2R)-3,3-Dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone hydrochloride

[Step 1] Preparation of [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone

To a solution of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone obtained in Reference Example 29 (5 g) in 2-propanol (50 mL) were added DIPEA (9.5 mL) and (2R)-3,3-dimethylbutan-2-amine (2.8 g), and the mixture was stirred at 100 °C overnight. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (6.0 g).

MS (m/z): 429 $[M+H]^+$

[0272]

[Step 2] Preparation of [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone hydrochloride

Analogous to the method in Example27, the title compound was synthesized by using [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone obtained in Step 1.

MS (m/z): 429 $[M-Cl]^+$

Elemental analysis value (for $C_{21}H_{28}N_6O_2S \cdot HCl + 0.5\ H_2O$)

Calculated value (%) C: 52.22, H: 6.14, N: 18.27

Found value (%) C: 52.09, H: 6.06, N: 18.26

[0273]

Example 63: Methyl (1-{[6-{[(2S)-1-hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using (2S)-2-amino-3,3-dimethylbutan-1-ol in place of (2R)-3-methylbutan-2-amine. MS (m/z): 502 $[M+H]^+$

[0274]

Example 64: Methyl [1-({6-[(3,3-dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

To a solution of methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 14 (25 mg) and 3,3-dimethylbutan-2-ol (61 mg) in THF (2 mL) was added 60 % sodium hydride (4 mg) under ice cooling, and the mixture was stirred at room temperature overnight. The reaction solution was diluted with ethyl acetate, separated by adding water, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound

(6 mg).

MS (m/z): 487 $[M+H]^+$

[0275]

Example 65: Methyl (1-{[6-(cyclobutyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 64, the title compound was synthesized by using cyclobutanol in place of 3,3-dimethylbutan-2-ol.

MS (m/z): 457 $[M+H]^+$

[0276]

Example 66: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)methanesulfonamide

Analogous to the method in Example 30 Step 3, the title compound was synthesized by using methanesulfonyl chloride in place of benzoyl chloride.

MS (m/z): 490 $[M+H]^+$

[0277]

Example 67: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanesulfonamide

Analogous to the method in Example 30 Step 3, the title compound was synthesized by using cyclopropanesulfonyl chloride in place of benzoyl chloride.
MS (m/z): 516 $[M+H]^+$

[0278]

Example 68: N-(1-{[6-{[(1S)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)ethanesulfonamide

Analogous to the method in Example 30 Step 3, the title compound was synthesized by using ethanesulfonyl chloride in place of benzoyl chloride.
MS (m/z): 504 $[M+H]^+$

[0279]

Example 69: N-(1-{[6-(tert-Butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methylpropanamide

To a solution of methyl 6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylate obtained in Example 36 Step 1 (280 mg) in 1,4-dioxane (3 mL) was added 2 M sodium hydroxide aqueous solution (1.27 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was neutralized with 2 M hydrochloric acid aqueous solution, and the reaction solution was concentrated under

reduced pressure to give a solid (50 mg). To a solution of the obtained solid in DMF (0.3 mL) were added DIPEA (41 mg), 2-methyl-N-(4-piperidyl)propanamide (which was prepared analogous to the method described in, for example, Bioorganic and Medicinal Chemistry Letters, 2012, 22, 3157-3162) (52 mg) and HATU (87 mg), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with chloroform and purified by silica gel column chromatography to give the title compound (28 mg).
MS (m/z): 470 $[M+H]^+$

[0280]

Example 70: N-(1-{[6-(tert-Butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2,2-difluoroacetamide

Analogous to the method in Example 69, the title compound was synthesized by using 2,2-difluoro-N-(4-piperidyl)acetamide obtained in Example 28 Step 1 in place of 2-methyl-N-(4-piperidyl)propanamide.
MS (m/z): 478 $[M+H]^+$

[0281]

Example 71: Ethyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-

yl)carbamate

Analogous to the method in Example 69, the title compound was synthesized by using ethyl piperidin-4-ylcarbamate (which was prepared analogous to the method described in, for example, US 19904918073) in place of 2-methyl-N-(4-piperidyl)propanamide.

MS (m/z): 472 $[M+H]^+$

[0282]

Example 72: [6-(tert-Butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyridin-2-ylamino)piperidin-1-yl]methanone

To a solution of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyridin-2-ylamino)piperidin-1-yl]methanone obtained in Reference Example 18 (25 mg) in NMP (0.5 mL) were added DIPEA (20 µL) and tert-butylamine (8 mg), and the mixture was stirred at 120 °C for 2 h. An additional tert-butylamine (8 mg) was added thereto, and the mixture was stirred at 120 °C for an additional hour. The reaction mixture was purified by silica gel column chromatography to give the title compound (8 mg).

MS (m/z): 477 $[M+H]^+$

[0283]

Example 73: Ethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of 6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 39 (50 mg) in DMF (0.3 mL) were added ethyl piperidin-4-ylcarbamate (which was prepared analogous to the method described in, for example, US 1990/4918073) (52 mg), DIPEA (59 mg) and HATU (87 mg), and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (30 mg).

MS (m/z): 484 $[M+H]^+$

[0284]

Example 74: Ethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate hydrochloride

Analogous to the method in Example 27, the title compound was synthesized by using ethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

obtained in Example 73.

MS (m/z): 484 $[M-Cl]^+$

Elemental analysis value (for $C_{23}H_{29}N_7O_3S \cdot HCl + 1.1H_2O$)

Calculated value (%) C: 51.17, H: 6.01, N: 18.16

Found value (%) C: 50.92, H: 6.12, N: 17.95

Example 75: [6-(tert-Butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone

Analogous to the method in Example 72, the title compound was synthesized by using [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone obtained in Reference Example 19 in place of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyridin-2-ylamino)piperidin-1-yl]methanone.

MS (m/z): 483 $[M+H]^+$

[0285]

Example 76: [6-(tert-Butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyrimidin-2-ylamino)piperidin-1-yl]methanone

Analogous to the method in Example 72, the title compound was synthesized by using [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-

(pyrimidin-2-ylamino)piperidin-1-yl]methanone obtained in Reference Example 20 in place of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyridin-2-ylamino)piperidin-1-yl]methanone.

MS (m/z): 478 $[M+H]^+$

[0286]

Example 77: Methyl (1-{[6-{[(1R)-1-(4-fluorophenyl)ethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Under argon atmosphere, to a solution of methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 14 (20 mg) in DMF (1 mL) were added DIPEA (25 μL) and (1R)-1-(4-fluorophenyl)ethanamine (18 μL), and the mixture was stirred at 80 °C for 4 h. The reaction solution was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (24 mg).

MS (m/z): 524 $[M+H]^+$

[0287]

Example 78: N-[1-({6-[(Azetidin-3-ylmethyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

To a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide obtained in Reference Example 15 (30 mg) in DMF (1 mL) were added DIPEA (48 µL) and 3-(aminomethyl)azetidine-1-carboxylic acid tert-butyl (19 mg), and the mixture was stirred at 120 °C for 2 h. The reaction solution was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give a solid (40 mg). To a solution of the obtained solid (35 mg) in dichloromethane (1 mL) was added TFA (1 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (29 mg).

MS (m/z): 481 $[M+H]^+$

[0288]

Example 79: N-(1-{[6-{[(1R)-1-(4-Fluorophenyl)ethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methylpropanamide

Analogous to the method in Example 77, the title compound was synthesized by using N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methylpropanamide obtained in Reference Example 16 in place of methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate.

MS (m/z): 536 $[M+H]^+$

[0289]

Example 80: Methyl [1-({6-[(2-methylbutan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using 2-methylbutan-2-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 472 $[M+H]^+$

[0290]

Example 81: (4-Hydroxypiperidin-1-yl)[6-(pentan-3-ylamino)-

2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone hydrochloride

[Step 1] Preparation of (4-hydroxypiperidin-1-yl)[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone

To a solution of (4-{[tert-butyl(dimethyl)silyl]oxy}piperidin-1-yl)[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone obtained in Reference Example 30 (840 mg) in 1-butanol (10 mL) were added DIPEA (1.2 mL) and pentan-3-amine (459 mg), and the mixture was stirred at 80 °C for 4 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give a solid (792 mg). To a solution of the obtained solid (790 mg) in THF (5 mL) was added 1 M tetrabutylammonium fluoride (THF solution, 6.0 mL), and the mixture was stirred at room temperature for 3 h. To the reaction solution was added saturated aqueous aqueous ammonium chloride, the solution was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (474 mg).

MS (m/z): 415 $[M+H]^+$

[Step 2] Preparation of (4-Hydroxypiperidin-1-yl)[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone hydrochloride

To a solution of (4-hydroxypiperidin-1-yl)[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone obtained in Step 1 (474 mg) in ethyl acetate (10 mL) was added 4 M hydrogen chloride-ethyl acetate solution (0.57 mL). The reaction solution was concentrated under reduced pressure to give the title compound (517 mg).

MS (m/z): 415 $[M-Cl]^+$

Elemental analysis value (for $C_{20}H_{26}N_6O_2S \cdot HCl + 0.5\ H_2O$)

Calculated value (%) C: 52.22, H: 6.14, N: 18.27

Found value (%) C: 52.09, H: 6.06, N: 18.26

[0291]

Example 82: Propyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Propyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 23 (30 mg) was dissolved in NMP (0.5 mL), to the mixture were added DIPEA (17 mg) and tert-butylamine (14 mg), and the mixture was stirred at 130 °C for 3 h in a sealed tube. The reaction solution was concentrated under reduced pressure, and the resulting

residue was purified by silica gel column chromatography to give the title compound (25 mg).

MS (m/z): 486 $[M+H]^+$

[0292]

Example 83: Propyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 82, the title compound was synthesized by using (1R)-1-cyclopropylethanamine in place of tert-butylamine.

MS (m/z): 498 $[M+H]^+$

[0293]

Example 84: Propyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 82, the title compound was synthesized by using (1S)-1-cyclopropylethanamine in place of tert-butylamine.

MS (m/z): 498 $[M+H]^+$

[0294]

Example 85: Propyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 82, the title compound was synthesized by using (2R)-3,3-dimethylbutan-2-amine in place of tert-butylamine.

MS (m/z): 514 $[M+H]^+$

[0295]

Example 86: Propyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 82, the title compound was synthesized by using (2S)-3,3-dimethylbutan-2-amine in place of tert-butylamine.

MS (m/z): 514 $[M+H]^+$

[0296]

Example 87: Methyl [1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate hydrochloride

[Step 1] Preparation of methyl [1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using 2,2-dimethylpropan-1-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 472 $[M+H]^+$

[Step 2] Preparation of methyl [1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate hydrochloride

To a solution of methyl [1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate obtained in Step 1 (48 mg) in ethyl acetate (3 mL) was added 4 M hydrogen chloride-ethyl acetate solution (50 µL). The reaction solution was concentrated under reduced pressure, and dried to give the title compound (51 mg).

MS (m/z): 472 $[M-Cl]^+$

Elemental analysis value (for $C_{22}H_{29}N_7O_3S \cdot HCl + 1.6\ H_2O$)

Calculated value (%) C: 49.22, H: 6.23, N: 18.26

Found value (%) C: 49.03, H: 6.03, N: 18.35

[0297]

Example 88: 2-Methoxyethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of 2-methoxyethyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference

Example 24 (20 mg) in ethanol (1 mL) were added DIPEA (30 µL) and (1R)-1-cyclopropylethanamine (14 µL), and the mixture was stirred at 80 °C overnight. The reaction mixture was purified by silica gel column chromatography to give the title compound (15 mg).

MS (m/z): 514 $[M+H]^-$

[0298]

Example 89: 2-Methoxyethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 88, the title compound was synthesized by using (1S)-1-cyclopropylethanamine in place of (1R)-1-cyclopropylethanamine.

MS (m/z): 514 $[M+H]^+$

[0299]

Example 90: 2-Methoxyethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 88, the title compound was synthesized by using (2R)-3,3-dimethylbutan-2-amine in place of (1R)-1-cyclopropylethanamine.

MS (m/z): 530 $[M+H]^+$

[0300]

Example 91: 2-Methoxyethyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 88, the title compound was synthesized by using (2S)-3,3-dimethylbutan-2-amine in place of (1R)-1-cyclopropylethanamine.

MS (m/z): 530 $[M+H]^+$

[0301]

Example 92: N-(1-{[6-{[(1R)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide

To a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide obtained in Reference Example 27 (50 mg) in 2-propanol (1 mL) were added DIPEA (60 µL) and (1R)-1-cyclopropylethanamine (49 mg), and the mixture was stirred at 90 °C for 3h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (42 mg).

MS (m/z): 484 $[M+H]^+$

[0302]

Example 93: N-(1-{[6-{[(2R)-3,3-Dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide

Analogous to the method in Example 92, the title compound was synthesized by using (2R)-3,3-dimethylbutan-2-amine in place of (1R)-1-cyclopropylethanamine.

MS (m/z): 500 $[M+H]^+$

[0303]

Example 94: (6-[(2,2-Dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}(4-hydroxypiperidin-1-yl)methanone

To a solution of 6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carboxylic acid obtained in Reference Example 49 (27 mg) in DMF (0.5 mL) were added piperidin-4-ol (16 mg), DIPEA (28 µL) and HATU (62 mg), and the mixture was stirred at room temperature overnight. Then, HATU (15 mg) was added thereto, and the mixture was stirred at room temperature for 3 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (16 mg).

MS (m/z): 415 $[M+H]^+$

[0304]

Example 95: Methyl [1-({6-[{[1-(methoxymethyl)cyclopropyl]methyl}(methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using 1-(1-(methoxymethyl)cyclopropyl)-N-methylmethanamine hydrochloride obtained in Reference Example 13 in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 514 $[M+H]^+$

[0305]

Example 96: 2,2-Difluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate hydrochloride

[Step 1] Preparation of 2,2-difluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of 2,2-difluoroethyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 25 (20 mg) in ethanol (1 mL) were added DIPEA (29 µL) and (1R)-1-cyclopropylethanamine (14 µL), and the mixture was stirred at 80 °C overnight. The reaction

mixture was purified by silica gel column chromatography to give the title compound (14 mg).

MS (m/z): 520 $[M+H]^+$

[Step 2] Preparation of 2,2-difluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate hydrochloride

To a solution of 2,2-difluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Step 1 (490 mg) in ethyl acetate was added 4 M hydrogen chloride-ethyl acetate solution (0.47 mL). The reaction solution was concentrated under reduced pressure, and the resulting residue was washed with diethyl ether to give the title compound (455 mg).

MS (m/z): 520 $[M-Cl]^+$

Elemental analysis value (for $C_{23}H_{27}F_2N_7O_3S \cdot HCl + 2.5\ H_2O$)

Calculated value (%) C: 45.96, H: 5.53, N: 16.31

Found value (%) C: 46.19, H: 5.34, N: 16.08

[0306]

Example 97: 2,2-Difluoroethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

hydrochloride

Analogous to the method in Example 96 Steps 1 and 2, the title compound was synthesized by using (2R)-3,3-dimethylbutan-2-amine in place of (1R)-1-cyclopropylethanamine.

MS (m/z): 536 $[M-Cl]^+$

Elemental analysis value (for $C_{24}H_{31}F_2N_7O_3S \cdot HCl + 1.1\ H_2O$)

Calculated value (%) C: 48.70, H: 5.82, N: 16.56

Found value (%) C: 48.50, H: 5.69, N: 16.49

[0307]

Example 98: 2,2-Difluoroethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 96 Step 1, the title compound was synthesized by using (1S)-1-cyclopropylethanamine in place of (1R)-1-cyclopropylethanamine.

MS (m/z): 520 $[M+H]^+$

[0308]

Example 99: 2,2-Difluoroethyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 96 Step 1, the

title compound was synthesized by using (2S)-3,3-dimethylbutan-2-amine in place of (1R)-1-cyclopropylethanamine.

MS (m/z): 536 $[M+H]^+$

[0309]

Example 100: tert-Butyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of tert-butyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 17 (200 mg) in 1-butanol (1 mL) were added (2R)-3,3-dimethylbutan-2-amine (131 mg) and DIPEA (0.3 mL), and the mixture was stirred at 80 °C for 4 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (183 mg).

MS (m/z): 528 $[M+H]^+$

[0310]

Example 101: 2-Methoxyethyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of 2-methoxyethyl (1-{[6-chloro-2-

(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 24 (20 mg) in ethanol (0.5 mL) were added DIPEA (45 µL) and tert-butylamine (23 µL), and the mixture was stirred at 130 °C for 4 h in a sealed tube. The reaction mixture was purified by silica gel column chromatography to give the title compound (2.4 mg).

MS (m/z): 502 $[M+H]^+$

[0311]

Example 102: 2-(Dimethylamino)ethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 40, the title compound was synthesized by using 2-(dimethylamino)ethyl piperidin-4-ylcarbamate obtained in Reference Example 52 in place of ethyl piperidin-4-ylcarbamate.

MS (m/z): 543 $[M+H]^+$

[0312]

Example 103: 2,2,2-Trifluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of 2,2,2-trifluoroethyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 26 (15 mg) in DMF (1 mL) were added DIPEA (21 μL) and (1R)-1-cyclopropylethanamine (10 μL), and the mixture was stirred at 90 °C for 3h. The reaction mixture was purified by silica gel column chromatography to give the title compound (5 mg).

MS (m/z): 538 $[M+H]^+$

[0313]

Example 104: 2,2,2-Trifluoroethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 103, the title compound was synthesized by using (2R)-3,3-dimethylbutan-2-amine in place of (1R)-1-cyclopropylethanamine.

MS (m/z): 554 $[M+H]^+$

[0314]

Example 105: N-(1-{[6-(Cyclopentyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 43, the title compound was synthesized by using cyclopentanol in place of cyclopropylmethanol.

MS (m/z): 481 $[M+H]^+$

[0315]

Example 106: 2-Methoxy-N-(1-{[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide

Analogous to the method in Example 92, the title compound was synthesized by using pentan-3-amine in place of (1R)-1-cyclopropylethanamine.

MS (m/z): 486 $[M+H]^+$

[0316]

Example 107: N-(1-{[6-(2-Ethylbutoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Under argon atmosphere, to a suspension of 60 % sodium hydride (4 mg) in THF (1.0 mL) were added 2-ethylbutan-1-ol (29 µL) and N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide obtained in Reference Example 15 (20 mg) in this sequence, and the mixture was stirred at room temperature overnight. To the reaction mixture was added water, the solution was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The

resulting residue was purified by silica gel column chromatography to give the title compound (16 mg).

MS (m/z): 496 $[M+H]^+$

[0317]

Example 108: Methyl (1-{[6-(pentan-3-yloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Under argon atmosphere, to a suspension of 60 % sodium hydride (4 mg) in THF (1 mL) were added pentan-3-ol (29 µL) and methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 14 (20 mg) in this sequence, and the mixture was stirred at room temperature for 3 h. An additional 60 % sodium hydride (4 mg) was added thereto, and the mixture was stirred further at room temperature overnight. To the reaction mixture was added water, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (15 mg).

MS (m/z): 473 $[M+H]^+$

[0318]

Example 109: Methyl (1-{[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using pentan-3-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 472 $[M+H]^+$

[0319]

Example 110: N-[1-({6-[(2-Ethylbutyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using the title compound was synthesized by using 2-ethylbutan-1-amine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 496 $[M+H]^+$

[0320]

Example 111: N-(1-{[6-(Pentan-3-yloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 107, the title compound was synthesized by using pentan-3-ol in place of

2-ethylbutan-1-ol.

MS (m/z): 483 $[M+H]^+$

[0321]

Example 112: Methyl [1-({6-[methyl(pentan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using N-methylpentan-3-amine hydrochloride in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 486 $[M+H]^+$

[0322]

Example 113: Methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 24, the title compound was synthesized by using (2R)-N,3,3-trimethylbutan-2-amine hydrochloride obtained in Reference Example 12 in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 500 $[M+H]^+$

[0323]

Example 114: N-(1-{[6-(2-Ethylbutoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-

yl)propanamide

Under argon atmosphere, to a suspension of 60 % sodium hydride (8.0 mg) in THF (1.0 mL) was added 2-ethylbutan-1-ol (49 mg) under ice cooling, and the mixture was stirred at room temperature for 5 min. Then, N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide obtained in Reference Example 31 (40 mg) was added thereto, and the mixture was stirred at room temperature overnight. To the reaction mixture was added water, and the solution was separated by ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (33 mg).

MS (m/z): 485 $[M+H]^+$

[0324]

Example 115: N-(1-{[6-{[(2R)-3,3-Dimethylbutan-2-yl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide

To a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide obtained in Reference Example 31 (20 mg) in

1-butanol (1 mL) were added DIPEA (50 µL) and (2R)-N,3,3-trimethylbutan-2-amine hydrochloride obtained in Reference Example 12 (14 mg), and the mixture was stirred at 80 °C for 7 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (9 mg).
MS (m/z): 498 $[M+H]^+$

[0325]

Example 116: N-[1-({6-[Methyl(pentan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide

Analogous to the method in Example 115, the title compound was synthesized by using N-methylpentan-3-amine hydrochloride in place of (2R)-N,3,3-trimethylbutan-2-amine hydrochloride.
MS (m/z): 484 $[M+H]^+$

[0326]

Example 117: 1-({6-[(4-Hydroxypiperidin-1-yl)carbonyl]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}amino)cyclopropanecarbonitrile hydrochloride

To a solution of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone obtained in Reference Example 29 (20 mg) in ethanol (0.2 mL) were added DIPEA (12 µL) and 1-amino-

cyclopropanecarbonitrile hydrochloride (65 mg), and the mixture was reacted in a microwave reactor at 130 °C for 1 h. The reaction mixture was purified by silica gel column chromatography to give a solid (16 mg). To a solution of the obtained solid (16 mg) in ethyl acetate (0.5 mL) was added 4 M hydrogen chloride-ethyl acetate solution (16 µL), and the solvent was distilled off under reduced pressure. The residue was triturated with ethyl acetate and hexane, and the powder was collected on a filter, and dried to give the title compound (12 mg).

MS (m/z): 410 $[M-Cl]^+$

[0327]

Example 118: [6-{[(2R)-3,3-Dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone

To a solution of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone obtained in Reference Example 32 (10 mg) in 1-butanol (1 mL) were added DIPEA (15 µL) and (2R)-3,3-dimethylbutan-2-amine (7 mg), and the mixture was stirred at 80 °C for 5 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (11 mg).

MS (m/z): 523 $[M+H]^+$

[0328]

Example 119: N-[1-({6-[(2-Methoxy-2-methylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide

Analogous to the method in Example 115, the title compound was synthesized by using 2-methoxy-2-methylpropan-1-amine in place of (2R)-N,3,3-trimethylbutan-2-amine hydrochloride.

MS (m/z): 486 $[M+H]^+$

[0329]

Example 120: (4-Hydroxypiperidin-1-yl){6-[methyl(pentan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}methanone hydrochloride

Analogous to the method in Example 117, the title compound was synthesized by using N-methylpentan-3-amine hydrochloride in place of 1-amino-cyclopropanecarbonitrile hydrochloride.

MS (m/z): 429 $[M-Cl]^+$

[0330]

Example 121: N-(1-{[6-{[(2R)-3-Methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl]carbonyl}piperidin-4-yl)propanamide

Analogous to the method in Example 115, the title compound was synthesized by using (2R)-3-methylbutan-2-amine in place of (2R)-N,3,3-trimethylbutan-2-amine hydrochloride.

MS (m/z): 470 $[M+H]^+$

[0331]

Example 122: N-(1-{[6-{[(2R)-3-Methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using (2R)-3-methylbutan-2-amine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 482 $[M+H]^+$

[0332]

Example 123: N-(1-{[6-{[(2S)-3-Methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using (2S)-3-methylbutan-2-amine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 482 $[M+H]^+$

[0333]

Example 124: N-(1-{[6-(Pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using pentan-3-amine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 482 $[M+H]^+$

[0334]

Example 125: Methyl [1-({6-[(2S)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate hydrochloride

Analogous to the method in Example 24 Steps 1 and 2, the title compound was synthesized by using (2S)-butan-2-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 458 $[M-Cl]^+$

Elemental analysis value (for $C_{21}H_{27}N_7O_3S \cdot HCl$)

Calculated value (%) C: 51.06, H: 5.71, N: 19.85

Found value (%) C: 51.00, H: 5.73, N: 19.74

Specific rotation $[\alpha]_D^{25}$=2.2 (c=2.00,DMSO)

[0335]

Example 126: Methyl [1-({6-[(2R)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-

yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 24 Steps 1, the title compound was synthesized by using (2R)-butan-2-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 458 $[M-H]^+$

[0336]

Example 127: Methyl [1-({6-[(2R)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate hydrochloride

Analogous to the method in Example 24 Steps 2, the title compound was synthesized by using methyl [1-({6-[(2R)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate obtained in Example 126 in place of methyl (1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate.

MS (m/z): 458 $[M-Cl]^+$

Elemental analysis value (for $C_{21}H_{27}N_7O_3S \cdot HCl + 0.7\ H_2O$)

Calculated value (%) C: 49.79, H: 5.85, N: 19.35

Found value (%) C: 49.73, H: 5.75, N: 19.44

Specific rotation $[\alpha]_D^{25}$=-1.8 (c=2.00,DMSO)

[0337]

Example 128: N-[1-({6-[(1-Methylcyclopropyl)amino]-2-

(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide

Analogous to the method in Example 115, the title compound was synthesized by using 1-methylcyclopropanamine hydrochloride (which was prepared analogous to the method described in, for example, Chemische Berichte, 1986, 119, 3672-3693) in place of (2R)-N,3,3-trimethylbutan-2-amine hydrochloride.

MS (m/z): 454 $[M+H]^+$

[0338]

Example 129: [6-{[(2R)-3,3-Dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(5-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone

Analogous to the method in Example 118, the title compound was synthesized by using [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(5-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone obtained in Reference Example 34 in place of [6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone.

MS (m/z): 523 $[M+H]^+$

[0339]

Example 130: 2-Methyl-N-[1-({6-[(2-methylbutan-2-yl)amino]-

2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide

To a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methylpropanamide obtained in Reference Example 16 (25 mg) in DMF (1 mL) were added DIPEA (50 µL) and 2-methylbutan-2-amine (25 mg), and the mixture was stirred at 120 °C for 1 h. Then, an additional 2-methylbutan-2-amine (25 mg) was added thereto, and the mixture was stirred at 120 °C for 1 h. To the reaction solution was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The reaction mixture was purified by silica gel column chromatography to give the title compound (12 mg).
MS (m/z): 484 $[M+H]^+$

[0340]

Example 131: N-[1-({6-[(2S)-Butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide

Analogous to the method in Example 115, the title compound was synthesized by using (2S)-butan-2-amine in place of (2R)-N,3,3-trimethylbutan-2-amine hydrochloride.

MS (m/z): 456 $[M+H]^+$

[0341]

Example 132: Methyl [1-({6-[tert-butyl(methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate hydrochloride

To a solution of methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 14 (50 mg) in NMP (0.1 mL) were added DIPEA (103 µL) and N,2-dimethylpropan-2-amine (31 mg), and the mixture was stirred at 150 °C for 2 h in a sealed tube. The reaction mixture was purified by silica gel column chromatography to give a solid (20 mg). To a solution of the obtained solid (20 mg) in ethyl acetate (2 mL) was added 4 M hydrogen chloride-ethyl acetate solution (15 µL). The reaction mixture was concentrated under reduced pressure to give the title compound (18 mg).

MS (m/z): 472 $[M-Cl]^+$

[0342]

Example 133: {6-[tert-Butyl(ethyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}(4-hydroxypiperidin-1-yl)methanone

[Step 1] Preparation of (4-{[tert-

butyl(dimethyl)silyl]oxy}piperidin-1-yl){6-[tert-butyl(ethyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}methanone

To a solution of (4-{[tert-butyl(dimethyl)silyl]oxy}piperidin-1-yl)[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone obtained in Reference Example 30 (150 mg) in ethanol (1 mL) were added DIPEA (706 µL) and tert-butylamine (333 µL), and the mixture was stirred in a microwave reactor at 150 °C for 1 h. An additional tert-butylamine (333 µL) was added thereto, and the mixture was further stirred in a microwave reactor at 150 °C for an additional hour. The reaction mixture was purified by silica gel column chromatography to give a solid (111 mg). To a solution of the obtained solid (30 mg) in DMF (0.6 mL) was added 60 % sodium hydride (12 mg) under ice cooling, and the mixture was stirred at room temperature for 15 min. To the mixture was added iodoethane (28 µL), and the mixture was stirred at room temperature overnight. To the reaction solution was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (28 mg).

^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 1.22-1.26 (4H, m), 1.57-1.63 (1H, m), 1.68 (9H, s), 1.82-1.90 (2H, m), 3.51-3.59 (1H, m), 3.63 (2H, q), 3.72-3.90 (3H, m), 4.01-4.09 (1H, m), 6.55 (1H, s), 6.97 (1H, s), 7.82 (1H, s), 8.41 (1H, s)

[Step 2] Preparation of {6-[tert-butyl(ethyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}(4-hydroxypiperidin-1-yl)methanone

To a solution of (4-{[tert-butyl(dimethyl)silyl]oxy}piperidin-1-yl){6-[tert-butyl(ethyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}methanone obtained in Step 1 (28 mg) in THF (0.5 mL) was added 1 M tetrabutylammonium fluoride (THF solution, 152 µL), and the mixture was stirred at room temperature overnight. To the reaction solution was added water, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (20 mg).

MS (m/z): 429 $[M+H]^+$

[0343]

Example 134: Cyclopropyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of cyclopropyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 21 (25 mg) in DMF (1 mL) were added DIPEA (19 µL) and (1S)-1-cyclopropylethanamine (7 mg), and the mixture was stirred at 100 °C for 1 h. The reaction solution was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, the aqueous layer was further extracted with ethyl acetate, and the combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (23 mg).

MS (m/z): 496 $[M+H]^+$

[0344]

Example 135: Cyclopropyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 134, the title compound was synthesized by using tert-butylamine in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 484 $[M+H]^+$

[0345]

Example 136: 2,2-Difluoro-N-(1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide

To a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2,2-difluoroacetamide obtained in Reference Example 28 (30 mg) in 2-propanol (2 mL) were added DIPEA (47 µL) and (2R)-3-methylbutan-2-amine (18 mg), and the mixture was stirred at 80 °C for 3 h. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (32 mg).

MS (m/z): 492 $[M+H]^+$

[0346]

Example 137: 3-[1-({6-[(2,2-Dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]-1,1-dimethylurea

To a solution of 3-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-1,1-dimethylurea obtained in Reference Example 33 (20 mg) in DMF (1 mL) were added DIPEA (32 µL) and 2,2-

dimethylpropan-1-amine (12 mg), and the mixture was stirred at 60 °C for 4 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (21 mg).

MS (m/z): 485 $[M+H]^+$

[0347]

Example 138: 3-(1-{[6-{[(1R)-1-Cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-1,1-dimethylurea

Analogous to the method in Example 137, the title compound was synthesized by using (1R)-1-cyclopropylethanamine in place of 2,2-dimethylpropan-1-amine.

MS (m/z): 483 $[M+H]^-$

[0348]

Example 139: Propan-2-yl [1-({6-[(3-methyloxetan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 29, the title compound was synthesized by using 3-methyloxetan-3-amine hydrochloride in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 500 $[M+H]^+$

[0349]

Example 140: Methyl [1-({6-[(dicyclopropylmethyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using dicyclopropylmethanamine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 496 $[M+H]^+$

[0350]

Example 141: Methyl (1-{[6-phenoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of phenol (34 mg) in THF (3 mL) was added 60 % sodium hydride (6 mg) under ice cooling, and the mixture was stirred for 5 min. Then, methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 14 (30 mg) was added thereto and the mixture was stirred at 70 °C overnight. To the reaction solution was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated

under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (19 mg).

MS (m/z): 479 $[M+H]^+$

[0351]

Example 142: tert-Butyl 4-{[6-({4-[(methoxycarbonyl)amino]piperidin-1-yl}carbonyl)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]amino}piperidine-1-carboxylate

To a solution of methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 14 (100 mg) in 2-propanol (2.0 mL) were added DIPEA (144 µL) and tert-butyl 4-aminopiperidine-1-carboxylate (143 mg), and the mixture was reacted in a microwave reactor at 150 °C for 1 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (105 mg).

MS (m/z): 585 $[M+H]^+$

[0352]

Example 143: Methyl (1-{[6-(piperidin-4-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate dihydrochloride

To a solution of tert-butyl 4-{[6-({4-

[(methoxycarbonyl)amino]piperidin-1-yl}carbonyl)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]amino}piperidine-1-carboxylate obtained in Example 142 (98 mg) was added 2 M hydrogen chloride-methanol solution, and the mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, the resulting residue was triturated with ethyl acetate, and the powder was collected on a filter, and dried to give the title compound (91 mg).

MS (m/z): 485[M-2Cl-H]$^+$

[0353]

Example 144: Methyl [1-({6-[(1-cyanocyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 142, the title compound was synthesized by using 1-aminocyclopropanecarbonitrile hydrochloride in place of tert-butyl 4-aminopiperidine-1-carboxylate.

MS (m/z): 467 [M+H]$^+$

[0354]

Example 145: Methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-

yl)carbamate

Under argon atmosphere, to a solution of methyl (1-{[6-chloro-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 35 (15 mg) in 2-propanol (1 mL) were added TEA (19 µL) and (1S)-1-cyclopropylethanamine (6 mg), and the mixture was stirred at 100 °C overnight. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (16 mg).

MS (m/z): 500 $[M+H]^+$

[0355]

Example 146: Methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 145, the title compound was synthesized by using (2R)-3,3-dimethylbutan-2-amine in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 516 $[M+H]^+$

[0356]

Example 147: tert-Butyl (3S)-3-{[6-({4-[(methoxycarbonyl)amino]piperidin-1-yl}carbonyl)-2-

(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]amino}pyrrolidine-1-carboxylate

Analogous to the method in Example 142, the title compound was synthesized by using (S)-3-aminopyrrolidine-1-carboxylic acid tert-butyl in place of tert-butyl 4-aminopiperidine-1-carboxylate.

MS (m/z): 571 $[M+H]^+$

[0357]

Example 148: tert-Butyl (3R)-3-{[6-({4-[(methoxycarbonyl)amino]piperidin-1-yl}carbonyl)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]amino}pyrrolidine-1-carboxylate

Analogous to the method in Example 142, the title compound was synthesized by using tert-butyl (R) -3-aminopyrrolidine-1-carboxylic acid in place of tert-butyl 4-aminopiperidine-1-carboxylate.

MS (m/z): 571 $[M+H]^+$

[0358]

Example 149: Methyl [1-({2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-[(3S)-pyrrolidin-3-ylamino]pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate dihydrochloride

Analogous to the method in Example 143, the title compound was synthesized by using tert-butyl (3S)-3-{[6-

({4-[(methoxycarbonyl)amino]piperidin-1-yl}carbonyl)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]amino}pyrrolidine-1-carboxylate obtained in Example 147. MS (m/z): 471[M-2Cl-H]$^+$

[0359]

Example 150: Methyl [1-({2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-[(3R)-pyrrolidin-3-ylamino]pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate dihydrochloride

Analogous to the method in Example 143, the title compound was synthesized by using tert-butyl (3R)-3-{[6-({4-[(methoxycarbonyl)amino]piperidin-1-yl}carbonyl)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]amino}pyrrolidine-1-carboxylate obtained in Example 148. MS (m/z): 471[M-2Cl-H]$^+$

[0360]

Example 151: Methyl (1-{[6-{[(3R)-1-methylpyrrolidin-3-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of methyl [1-({2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-[(3R)-pyrrolidin-3-ylamino]pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate dihydrochloride obtained in Example 150 (20 mg) in methanol (0.2 mL) were added 2-picoline borane complex (40 mg), 37 %

formaldehyde aqueous solution (30 µL) and acetic acid (20 µL), and the mixture was stirred at room temperature overnight. The reaction mixture was purified by silica gel column chromatography to give the title compound (7 mg).

MS (m/z): 485 $[M+H]^+$

[0361]

Example 152: Methyl (1-{[6-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of methyl [1-({2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-[(3R)-pyrrolidin-3-ylamino]pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate dihydrochloride obtained in Example 150 (20 mg) in THF (0.5 mL) were added triethylamine (51 µL) and acetyl chloride (26 µL) under ice cooling, and the mixture was stirred at room temperature for 3 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (8 mg).

MS (m/z): 513 $[M+H]^+$

[0362]

Example 153: Methyl [1-({6-[(2S)-butan-2-ylamino]-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate

Analogous to the method in Example 145, the title compound was synthesized by using (2S)-butan-2-amine in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 488 $[M+H]^+$

[0363]

Example 154: Methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Under argon atmosphere, methyl (1-{[6-chloro-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 36 (10 mg) in 2-propanol (1 mL) were added TEA (12 µL) and (1S)-1-cyclopropylethanamine (4 mg), and the mixture was stirred at 100 °C overnight. The reaction solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography to give the title compound (5 mg).

MS (m/z): 514 $[M+H]^+$

[0364]

Example 155: Methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

Analogous to the method in Example 154, the title compound was synthesized by using (2R)-3,3-dimethylbutan-2-amine in place of (1S)-1-cyclopropylethanamine.

MS (m/z): 530 $[M+H]^+$

[0365]

Example 156: Methyl (1-{[2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-(pyridin-3-yloxy)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of pyridin-3-ol (34 mg) in DMF (1.5 mL) was added 60 % sodium hydride (9.0 mg) under ice cooling, and the mixture was stirred for 5 min. Then, methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Reference Example 14 (30 mg) was added thereto, and the mixture was stirred at room temperature for 30 min. The reaction mixture was purified by silica gel column chromatography to give the title compound (23 mg).

MS (m/z): 480 $[M+H]^+$

[0366]

Example 157: N-(1-{[6-(2-ethylpiperidin-1-yl)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

To a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-

b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide obtained in Reference Example 15 (15 mg) in 1-butanol (1 mL) were added DIPEA (151 µL) and 2-ethylpiperidin (79 mg), and the mixture was reacted in a microwave reactor at 170 °C for 1 h. The reaction mixture was purified by silica gel column chromatography to give the title compound (18 mg).

MS (m/z): 508 $[M+H]^+$

[0367]

Example 158: Methyl (1-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-[(2,2,2-trifluoroethyl)amino]pyrimidine-4-carbonylpiperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using 2,2,2-trifluoroethan-1-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 484 $[M+H]^+$

[0368]

Example 159: N-1-[2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-[(thiophen-2-yl)methyl]aminopyrimidine-4-carbonyl]piperidin-4-ylcyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using thiophen-2-ylmethanamine

in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 508 $[M+H]^+$

[0369]

Example 160: N-1-[6-[(furan-2-yl)methyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using furan-2-ylmethanamine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 492 $[M+H]^+$

[0370]

Example 161: Methyl 1-[6-[(1R)-1-cyclohexylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using (1R)-1-cyclohexylethan-1-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 512 $[M+H]^+$

[0371]

Example 162: Methyl 1-[2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-[1-(pyridin-4-yl)ethyl]aminopyrimidine-4-

carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using 1-(pyridin-4-yl)ethan-1-amine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 507 $[M+H]^+$

[0372]

Example 163: Methyl (1-6-[(2-cyclopropylethyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using 2-cyclopropylethanamine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 470 $[M+H]^+$

[0373]

Example 164: Tert-butyl 3-([6-4-[(methoxycarbonyl)amino]piperidine-1-carbonyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]oxymethyl)azetidine-1-carboxylate

Analogous to the method in Example 64, the title compound was synthesized by using Tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate in place of 3,3-dimethylbutan-2-ol.

MS (m/z): 572 $[M+H]^+$

[0374]

Example 165: N-1-[6-[(1S)-1-cyclopropylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-yl cyclobutanecarboxamide

Analogous to the method in Example 30 Step 3, the title compound was synthesized by using cyclobutanecarbonyl chloride in place of benzoyl chloride.

MS (m/z): 494 $[M+H]^+$

[0375]

Example 166: N-1-[6-[(1S)-1-cyclopropylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclopentanecarboxamide

Analogous to the method in Example 30 Step 3, the title compound was synthesized by using cyclopentanecarbonyl chloride in place of benzoyl chloride.

MS (m/z): 508 $[M+H]^+$

[0376]

Example 167: N-1-[6-[(1S)-1-cyclopropylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclohexanecarboxamide

Analogous to the method in Example 30 Step 3, the

title compound was synthesized by using cyclohexanecarbonyl chloride in place of benzoyl chloride.

MS (m/z): 522 $[M+H]^+$

[0377]

Example 168: N-(1-6-[(trans-4-hydroxycyclohexyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using trans-4-aminocyclohexan-1-ol in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 510 $[M+H]^+$

[0378]

Example 169: N-1-[6-[(1R)-1-cyclohexylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using (1R)-1-cyclohexylethan-1-amine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 522 $[M+H]^+$

[0379]

Example 170: N-1-[2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-[1-(pyridin-4-yl)ethyl]aminopyrimidine-4-

carbonyl]piperidin-4-ylcyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using 1-(4-pyridyl)ethanamine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 517 $[M+H]^+$

[0380]

Example 171: Tert-butyl 4-[6-4-[(cyclopropanecarbonyl)amino]piperidine-1-carbonyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]aminopiperidine-1-carboxylate

Analogous to the method in Example 16, the title compound was synthesized by using tert-butyl 4-aminopiperidine-1-carboxylate in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 595 $[M+H]^+$

[0381]

Example 172: N-(1-6-[(oxan-4-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using tetrahydropyran-2-amine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 496 $[M+H]^+$

[0382]

Example 173: N-(1-6-[(oxetan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)cyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using oxetan-3-amine in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 468 $[M+H]^+$

[0383]

Example 174: Methyl (1-6-[(3-cyclopropyl-2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using 3-cyclopropyl-2,2-dimethylpropane-1-amine hydrochloride in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 512 $[M+H]^+$

[0384]

Example 175: Methyl 1-[6-([1-(methanesulfonyl)piperidin-4-yl]methylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

[Step 1] Preparation of tert-butyl 4-([6-4-

[(methoxycarbonyl)amino]piperidine-1-carbonyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]aminomethyl)piperidine-1-carboxylate

Analogous to the method in Example 24 Steps 1, the title compound was synthesized by using tert-butyl 4-(aminomethyl)piperidine-1-carboxylate in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 599 $[M+H]^+$

[Step 2] Preparation of methyl 1-[6-([1-(methanesulfonyl)piperidin-4-yl]methylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

To a solution of tert-butyl 4-([6-4-[(methoxycarbonyl)amino]piperidine-1-carbonyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]aminomethyl)piperidine-1-carboxylate obtained in Step 1 (115 mg) was added 2 M hydrogen chloride-methanol solution (2 mL), and the mixture was stirred at 40 °C for 5 h. The reaction solution was concentrated under reduced pressure, and the resulting residure was washed with ether, collected on a filter, and dried to give a solid compound (105 mg). The obtained solid compound (25 mg) was suspended in dichloromethane, and DIPEA (38 µL) and methanesulfonyl chloride (8 mg) were added, and the mixture was stirred

under ice cooling for 15 min. The reaction mixture was purified by silica gel column chromatography to give the title compound (17 mg).

MS (m/z): 577 $[M+H]^+$

[0385]

Example 176: N-1-[6-[(1R)-bicyclo[2.2.1]heptan-2-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclopropanecarboxamide

Analogous to the method in Example 16, the title compound was synthesized by using norbornene-2-amine hydrochloride in place of (2R)-3,3-dimethylbutan-2-amine.

MS (m/z): 506 $[M+H]^+$

[0386]

Example 177: Methyl (1-6-[(cis-4-hydroxycyclohexyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using cis-4-aminocyclohexanol in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 500 $[M+H]^+$

[0387]

Example 178: Methyl (1-6-[(trans-4-

hydroxycyclohexyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)carbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using trans-4-aminocyclohexanol in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 500 $[M+H]^+$

[0388]

Example 179: Methyl 1-[6-(cyclopentylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using cyclopentanamine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 470 $[M+H]^+$

[0389]

Example 180: Methyl 1-[6-(cyclohexylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 24 Step 1, the title compound was synthesized by using cyclohexanamine in place of (2R)-3-methylbutan-2-amine.

MS (m/z): 584 $[M+H]^+$

[0390]

Example 181: N-(1-6-[(piperidin-4-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)cyclopropanecarboxamide dihydrochloride

To a solution of tert-butyl 4-[6-4-[(cyclopropanecarbonyl)amino]piperidine-1-carbonyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]aminopiperidine-1-carboxylate obtained in Example 171 (55 mg) was added 2 M hydrogen chloride-methanol solution (3 mL), and the mixture was stirred at room temperature fo 2 h. The reaction solution was concentrated under reduced pressure, the resulting residue was triturated with diethyl ether, collected on a filter, and dried to give the title compound (52 mg).

MS (m/z): 495[M-2Cl-H]$^+$

[0391]

Example 182: N-1-[6-[(2R)-3,3-dimethylbutan-2-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclohexanecarboxamide

Analogous to the method in Example 40, the title compound was synthesized by using N-(piperidin-4-yl)cyclohexanecarboxamide hydrochloride in place of ethyl piperidin-4-ylcarbamate.

MS (m/z): 538 $[M+H]^+$

[0392]

Example 183: N-1-[6-[(2R)-3,3-dimethylbutan-2-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylbenzamide

Analogous to the method in Example 40, the title compound was synthesized by using N-(4-piperidyl)benzamide hydrochloride in place of ethyl piperidin-4-ylcarbamate.

MS (m/z): 532 $[M+H]^+$

[0393]

Example 184: N-1-[6-[(1S)-1-cyclopropylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-yl-2-methylbenzamide

Analogous to the method in Example 30 step 3, the title compound was synthesized by using 2-methylbenzoyl chloride in place of benzoyl chloride.

MS (m/z): 530 $[M+H]^+$

[0394]

Example 185: N-1-[6-[(1S)-1-cyclopropylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylpyridine-2-carboxamide

Analogous to the method in Example 30 step 3, the title compound was synthesized by using pyridine-2-carbonyl chloride hydrochloride in place of benzoyl chloride.

MS (m/z): 517 $[M+H]^+$

[0395]

Example 186: N-1-[6-[(1S)-1-cyclopropylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-yl-2-methoxybenzamide

Analogous to the method in Example 30 step 3, the title compound was synthesized by using 2-methoxybenzoyl chloride in place of benzoyl chloride.

MS (m/z): 546 $[M+H]^+$

[0396]

Example 187: N-1-[6-[(1S)-1-cyclopropylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylpyridine-4-carboxamide

Analogous to the method in Example 30 step 3, the title compound was synthesized by using pyridine-4-carbonyl chloride in place of benzoyl chloride.

MS (m/z): 517 $[M+H]^+$

[0397]

Example 188: N-(1-6-[(1-acetylpiperidin-4-yl)amino]-2-

(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)cyclopropanecarboxamide

Under argon atmosphere, to a solution of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide (30 mg) obtained in Reference Example 15 in 2-propanol (2 mL) were added DIPEA (48 µL) and 1-(4-amino-1-piperidyl)ethanone (15 mg), and the mixture was stirred at 90 °C for 1h. NMP (0.5 mL) was further added, and the mixture was stirred at 120 °C for 2h. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give a solid compound 1(30 mg).

MS (m/z): 537 $[M+H]^+$

[0398]

Example 189: N-1-[6-[1-(methanesulfonyl)piperidin-4-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclopropanecarboxamide

N-(1-6-[(piperidin-4-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)cyclopropanecarboxamide-dihydrochloride (20 mg) obtained in Example 181 was suspended in dichloromethane (2 mL), and DIPEA (30 µL) and methanesulfonyl chloride (6 mg) were added, and the mixture was stirred under ice cooling for 15

min. The reaction mixture was purified by silica gel column chromatography to give the title compound (12 mg).
MS (m/z): 573 $[M+H]^+$

[0399]

Example 190: N-1-[6-[(1S)-1-cyclopropylethyl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylpentanamide

Analogous to the method in Example 30 step 3, the title compound was synthesized by using valeroyl chloride in place of benzoyl chloride.
MS (m/z): 496 $[M+H]^+$

[0400]

Example 191: N-1-[6-[(3R)-1-(cyanoacetyl)pyrrolidin-3-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclopropanecarboxamide

Under argon atmosphere, to a solution of tert-butyl-[(3R)-pyrrolidin-3-yl]carbamate (500 mg) in THF (5 mL) were added ethyl cyanoacetate (607 mg) and (1,8-diazabicyclo[5.4.0]-7-undecene (204 mg), and the mixture was stirred at 40 °C for 2h. The reaction solution was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was extracted with ethyl acetate. The combined organic

layers were dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give a solid compound 1(530 mg). The obtained solid compound 1 (530 mg) was dissolved in 2M-hydrochloric acid-methanol solution (8 mL), and the mixture was stirred at at room temperature overnight. Et_2O was added to the reaction mixture, and the resulting precipitate was collected by filtration and dried to give a solid compound 2 (331 mg). N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4 yl)cyclopropanecarboxamide obtained in Reference Example 15 (30 mg) in NMP (1 mL) were added DIPEA (48 μL) and the above solid compound 2 (26 mg), and the mixture was stirred 120 °C for 3h. The reaction solution was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, washed with saturated brine, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (22 mg).

MS (m/z): 548 $[M+H]^+$

[0401]

Example 192: Methyl 4-([6-4-[(methoxycarbonyl)amino]piperidine-1-carbonyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]aminomethyl)piperidine-1-carboxylate

Analogous to the method in Example 175 step 2, the title compound was synthesized by using methyl chloroformate in place of methanesulfonyl chloride.

MS (m/z): 557 $[M+H]^+$

[0402]

Example 193: N-1-[6-[1-(propane-2-sulfonyl)piperidin-4-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclopropanecarboxamide

Analogous to the method in Example 189, the title compound was synthesized by using propane-2-sulfonyl chloride in place of methanesulfonyl chloride.

MS (m/z): 601 $[M+H]^+$

[0403]

Example 194: Methyl 4-[6-4-[(cyclopropanecarbonyl)amino]piperidine-1-carbonyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]aminopiperidine-1-carboxylate

Analogous to the method in Example 189, the title compound was synthesized by using methyl chloroformate in

place of methanesulfonyl chloride.

MS (m/z): 553 $[M+H]^+$

[0404]

Example 195: N-1-[6-[(2R)-3,3-dimethylbutan-2-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylheptanamide

[Step 1] Preparation of (4-Aminopiperidin-1-yl)[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl) pyrimidin-4-yl]methanone

tert-Butyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate obtained in Example 100 (305 mg) in dichloromethane (1 mL) was added TFA (1 mL), and the mixture was stirred at room temperature for 1h. The reaction solution was diluted with chloroform, neutralized with saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with chloroform. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (180 mg).

MS (m/z): 428 $[M+H]^+$

[Step 2] Preparation of N-1-[6-[(2R)-3,3-dimethylbutan-2-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylheptanamide

(4-Aminopiperidin-1-yl)[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl) pyrimidin-4-yl]methanone obtained in step 1 (10 mg) in dichloromethane (1 mL) were added DIPEA (16 µL) and heptanoyl chloride (4mg) under ice cooling, and the mixture was stirred at room temperature for 15 min. The reaction mixture was purified by silica gel column chromatography to give the title compound (18 mg).

MS (m/z): 540 $[M+H]^+$

[0405]

Example 196: 2-Chloro-N-1-[6-[(2R)-3,3-dimethylbutan-2-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylbenzamide

Analogous to the method in Example 195 Step 2, the title compound was synthesized by using 2-chlorobenzoyl chloride in place of heptanoyl chloride.

MS (m/z): 566, 568 $[M+H]^+$

[0406]

Example 197: N-1-[6-[(2R)-3,3-dimethylbutan-2-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-

carbonyl]piperidin-4-yl-4-fluorobenzamide

Analogous to the method in Example 195 Step 2, the title compound was synthesized by using 4-fluorobenzoyl chloride in place of heptanoyl chloride.

MS (m/z): 550 $[M+H]^+$

[0407]

Example 198: Methyl (1-6-[(1-propanoylpiperidin-4-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonylpiperidin-4-yl)carbamate

To a solution of Methyl (1-{[6-(piperidin-4-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate dihydrochloride obtained in Example 143 (15 mg) in THF (0.5 mL) were added TEA (38 µL) and propionyl chloride (17 mg), and the mixture was stirred at room temperature for 2h. The reaction solution was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (9 mg).

MS (m/z): 541 $[M+H]^+$

[0408]

Example 199: Methyl (1-{[6-{[1-(cyanoacetyl)piperidin-4-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate

To a solution of Methyl (1-{[6-(piperidin-4-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate dihydrochloride obtained in Example 143 (15 mg) in DMF (0.5 mL) were added cyanoacetic acid (5 mg), DIPEA (14 μL) and HATU (15 mg), and the mixture was stirred at room temperature overnight. The reaction solution was diluted with ethyl acetate, separated by adding saturated aqueous sodium bicarbonate solution, and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (3 mg).
MS (m/z): 552 $[M+H]^+$

[0409]

Example 200: Methyl 1-[6-[1-(methanesulfonyl)piperidin-4-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 198, the title compound was synthesized by using methanesulfonyl chloride

in place of propionyl chloride.

MS (m/z): 563 $[M+H]^+$

[0410]

Example 201: Methyl 1-[6-[(3R)-1-(cyanoacetyl)pyrrolidin-3-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 191, the title compound was synthesized by using methyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate in place of N-(1-{[6-Chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

MS (m/z): 538 $[M+H]^+$

[0411]

Example 202: N-1-[6-[(3R)-1-(cyanoacetyl)pyrrolidin-3-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylpropanamide

Analogous to the method in Example 191, the title compound was synthesized by using N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide in place of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide

MS (m/z): 536 $[M+H]^+$

[0412]

Example 203: Ethyl 1-[6-[(3R)-1-(cyanoacetyl)pyrrolidin-3-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 191, the title compound was synthesized by using ethyl (1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate in place of N-(1-{[6-chloro-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4 yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide.

MS (m/z): 552 $[M+H]^+$

[0413]

Example 204: N-1-[6-[(3S)-1-(cyanoacetyl)pyrrolidin-3-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcyclopropanecarboxamide

Analogous to the method in Example 191, the title compound was synthesized by using tert-butyl N-[(3S)-pyrrolidin-3-yl]carbamate in place of tert-butyl N-[(3R)-pyrrolidin-3-yl]carbamate.

MS (m/z): 548 $[M+H]^+$

[0414]

Example 205: Methyl 1-[6-[(3R)-1-(cyclopropanecarbonyl)pyrrolidin-3-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 152, the title compound was synthesized by using cyclopropanecarbonyl chloride in place of acetyl chloride.

MS (m/z): 539 $[M+H]^+$

[0415]

Example 206: Methyl 1-[6-[(3R)-1-(cyclobutanecarbonyl)pyrrolidin-3-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 152, the title compound was synthesized by using cyclobutanecarbonyl chloride in place of acetyl chloride.

MS (m/z): 553 $[M+H]^+$

[0416]

Example 207: Methyl 1-[6-[(3R)-1-butanoylpyrrolidin-3-yl]amino-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidine-4-carbonyl]piperidin-4-ylcarbamate

Analogous to the method in Example 152, the title compound was synthesized by using butyryl chloride in place

of acetyl chloride.

MS (m/z): 541 $[M+H]^+$

Test Example 1: Inhibitory effect on JAK tyrosine kinase

1. Preparation of test compound

The test compound was dissolved in dimethyl sulfoxide (DMSO) to 10 mM and further diluted with DMSO to the concentrations of 1000, 100, 10, 1, 0.1 and 0.01 μM, respectively. For JAK1, these solutions of the test compound at the six concentrations 10 mM, 1000 μM, 100 μM, 10 μM, 1 μM and 0.1 μM were used. For JAK2 and JAK3, these solutions of the test compound at the six concentrations 1000 μM, 100 μM, 10 μM, 1 μM, 0.1 μM and 0.01 μM were used. The test compound solutions were diluted further to 20-fold with an assay buffer to obtain a sample solution. 15 mM Tris-HCl (pH7.5), 0.01 (v/v) % Tween-20 and 1 mM dithiothreitol were used as an assay buffer. DMSO was diluted to 20-fold with the assay buffer and was used as a negative control.

[0417]

2. JAK tyrosine kinase inhibitory activity in the presence of 1 mM ATP

The activity was determined by ELISA method. Each of the sample solutions was added to a streptavidine coated

96-well plate (DELFIA Strip Plate 8 x 12 well, PerkinElmer) at 10 µL/well (n=2). A substrate solution containing biotinylated peptide substrate (1250 nM for JAK1, 625 nM for JAK2 and JAK3), 2.5 mM ATP (final concentration 1 mM), 25 mM $MgCl_2$, 15 mM Tris-HCl (pH 7.5), 0.01 (v/v) % Tween-20 and 1 mM dithiothreitol, was added to the plate at 20 µL/well. Finally, JAK tyrosine kinase (Carna Biosciences, Inc.), which was previously diluted with the assay buffer to 7.5 nM for JAK1 and 0.75 nM for JAK2 and JAK3, was added to the plate at 20 µL/well, and the plate was incubated at 30 °C for 1 h. The plate was washed four times with buffer (50 mM Tris-HCl (pH 7.5), 150 mM NaCl, 0.02 (v/v) % Tween-20). A blocking buffer (0.1 % Bovine Serum Albumin, 50 mM Tris-HCl (pH 7.5), 150 mM NaCl, 0.02 (v/v) % Tween-20) was added to the plate at 150 µL/well and the plate was blocked at 30 °C for 1 h. The blocking buffer was removed, and a horse radish peroxidase-labeled anti-phosphorylated tyrosine antibody (BD Biosciences, Inc.) (diluted to 10000-fold with the blocking buffer) was added to the plate at 100 µL/well, and the plate was incubated at 30 °C for 30 min. The plate was washed with the washing buffer four times, and 3,3',5,5'-tetramethylbenzidine solution (Nacalai Tesque) was added to the plate at 100 µL/well to develop the color for 10 minutes. To the plate was added 0.1 M sulfuric acid at 100 µL/well to stop the reaction. The

absorbance at 450 nm was measured using a microplate reader (BIO-RAD).

[0418]

3. Analysis of the results

A non-liner regression analysis using SAS system (SAS Institute Inc.) was performed for the absorbance as measured, and the concentration of the test compound that resulted in 50% inhibition of the respective tyrosine kinase activity (IC_{50}) was calculated. The results are shown in the following Tables 1 to 6.

[0419]

[Table 1]

Test Compound (Example)	JAK1 Inhibitory Activity (IC_{50}: nM)	JAK2 Inhibitory Activity (IC_{50}: nM)	JAK3 Inhibitory Activity (IC_{50}: nM)
1	52	3400	3400
2	570	2100	2700
3	62	1400	3200
4	210	730	3000
5	130	2500	1400
6	240	1800	2800
7	69	>10000	2700
8	52	2400	3800
9	19	960	2000
11	21	2500	4800
12	120	2200	1800
13	400	2400	1600
14	69	1700	1500
15	110	2500	7200
16	53	2200	2200
17	230	5100	5800
18	310	2300	1700
19	710	4400	6500
20	1400	4700	4200
21	230	2200	>10000
22	130	800	3700
23	860	870	3300
24	290	1500	4200
25	200	800	2000
26	75	2100	2100
27	140	2500	4300
28	120	2100	>10000
29	140	1200	3000
30	110	1400	>10000

[0420]

[Table 2]

Test Compound (Example)	JAK1 Inhibitory Activity (IC_{50}: nM)	JAK2 Inhibitory Activity (IC_{50}: nM)	JAK3 Inhibitory Activity (IC_{50}: nM)
32	380	1800	>10000
33	130	1700	1700
34	350	1900	3000
35	270	2400	>10000
36	86	620	>10000
37	240	1600	>10000
38	260	1200	>10000
39	140	1300	2900
41	96	2700	>10000
43	130	>10000	>10000
44	66	1300	>10000
45	310	5700	>10000
46	170	1600	7200
48	150	>10000	>10000
50	150	2000	2500
52	180	9300	>10000
55	140	>10000	>10000
56	940	7300	>10000
58	400	2900	>10000
59	140	3900	5600
60	72	5400	6100
61	540	>10000	9400
62	10	1000	1100
63	180	7300	10000
64	260	3100	>10000
65	130	3100	10000
66	110	620	2400
67	25	680	1900
68	73	790	2100
69	810	3500	5700

[0421]

[Table 3]

Test Compound (Example)	JAK1 Inhibitory Activity (IC_{50}: nM)	JAK2 Inhibitory Activity (IC_{50}: nM)	JAK3 Inhibitory Activity (IC_{50}: nM)
71	200	3700	4000
72	310	6100	5900
73	73	3200	2200
74	95	3100	2600
75	150	930	4800
77	980	3200	>10000
78	4100	>10000	>10000
79	870	3300	>10000
80	110	820	2300
81	1600	2200	3300
82	58	9700	5800
85	330	2200	2300
87	250	1600	9500
88	190	1000	4100
90	620	1200	1800
93	40	1200	1000
94	1900	2200	5400
96	250	1000	2200
97	210	1300	2700
98	37	1400	1400
99	19	790	2600
100	140	3000	3400
101	98	1800	3100
102	24	1300	1700
103	140	2400	5900
104	200	3000	3400
106	600	1300	2800
107	200	3500	1600
108	200	2500	>10000
109	190	1800	2400

[0422]

[Table 4]

Test Compound (Example)	JAK1 Inhibitory Activity (IC_{50}: nM)	JAK2 Inhibitory Activity (IC_{50}: nM)	JAK3 Inhibitory Activity (IC_{50}: nM)
110	78	880	>10000
111	120	2400	>10000
112	350	3500	2900
114	360	1200	2700
116	210	1900	3800
117	1400	>10000	5700
119	670	4200	>10000
120	870	3000	3400
123	260	1400	1600
124	220	1700	2200
125	210	4700	>10000
126	820	>10000	>10000
127	590	>10000	>10000
128	760	8500	>10000
131	310	2200	4700
132	790	>10000	>10000
133	2900	>10000	>10000
135	68	2400	3700
136	490	1400	3500
137	640	1400	4200
138	650	2000	4300
139	43	2900	2100
140	280	770	340
141	1100	>10000	>10000
142	1200	>10000	>10000
143	1900	>10000	>10000
144	480	>10000	6600
145	270	1200	1400
146	270	1600	1400
147	2600	>10000	>10000

[0423]

[Table 5]

Test Compound (Example)	JAK1 Inhibitory Activity (IC_{50}: nM)	JAK2 Inhibitory Activity (IC_{50}: nM)	JAK3 Inhibitory Activity (IC_{50}: nM)
148	1600	>10000	>10000
149	1000	>10000	>10000
150	5200	>10000	>10000
151	2600	>10000	>10000
152	2300	>10000	>10000
153	210	7200	9000
154	180	5300	3100
155	24	4600	1400
156	820	>10000	10000
157	310	5100	>10000
158	1300	>10000	>10000
159	2600	>10000	>10000
160	980	>10000	>10000
161	47	>10000	>10000
162	1100	>10000	>10000
163	450	>10000	5600
164	2600	>10000	>10000
165	40	>10000	1200
166	280	10000	1300
167	230	9500	1100
168	1200	>10000	3200
169	160	6400	2100
170	1600	>10000	>10000
171	850	>10000	>10000
172	320	>10000	>10000
173	3400	>10000	>10000
174	300	>10000	5600
175	96	>10000	>10000
176	78	4400	4600
177	300	>10000	>10000

[Table 6]

Test Compound (Example)	JAK1 Inhibitory Activity (IC_{50}: nM)	JAK2 Inhibitory Activity (IC_{50}: nM)	JAK3 Inhibitory Activity (IC_{50}: nM)
178	510	>10000	9500
179	320	>10000	>10000
180	560	>10000	>10000
181	860	>10000	>10000
182	88	5400	1700
183	87	>10000	1200
184	62	>10000	470
185	190	>10000	810
186	81	>10000	580
187	68	2100	1800
188	1300	>10000	>10000
189	1100	>10000	>10000
190	65	6600	1000
191	52	>10000	>10000
192	690	>10000	>10000
193	470	>10000	>10000
194	260	>10000	>10000
195	310	9000	4900
196	110	9100	7300
197	120	8200	3800
198	1500	>10000	>10000
199	2800	>10000	>10000
200	2400	>10000	>10000
201	120	>10000	>10000
202	300	>10000	>10000
203	70	>10000	>10000
204	2700	>10000	>10000
205	850	>10000	>10000
206	940	>10000	>10000
207	410	>10000	>10000

[0424]

Test Example 2: Inhibitory effect on *Aspergillus*-induced

airway inflammation model

Aspergillus fumigatus extracts (Greer laboratories, Inc.) were adjusted to 400 μg/mL with PBS. The *Aspergillus fumigatus* solutions thus prepared were administered to mice as nasal drops (50 μL) on Day 0, Day 1, Day 7 and Day 8. The nasal drop was administered one hour later of the administration of test compounds in the morning. The test compound was administered twice a day at morning and evening of Day 0 to Day 9. The test compound was suspended in 0.5 % methylcellulose at 10 mg/mL, and orally administered at the dosage of 10 mL/kg. The bronchoalveolar lavage fluid (BALF) was collected at Day 10, and the total white blood cell count in BALF was measured using Celltac (NIHON KOHDEN). The ratio of eosinophil in total white blood cell was calculated using ADVIA 120 (Siemens Healthcare Diagnostics), and the ratio was multiplied by the total white blood cell count to determine the eosinophil count in BALF. The inhibition rate of the test compound was determined, assuming the inhibitory ratio in the treatment with *Aspergillus fumigatus* extract and 0.5 % methylcellulose as 0 % and the inhibitory ratio in the treatment without *Aspergillus fumigatus* extract but with 0.5 % methylcellulose as 100 %. The results are shown in Table 7.

[0425]

[Table 7]

Test Compound (Example)	Inhibition rate on count of invasive eosinophil in BALF (%)
1	43
16	33
20	61
21	47
22	57
23	31
24	35
25	30
26	58
27	62
28	52
33	37
41	51
58	37
62	36
73	64
74	34
81	43
87	24
96	51
97	43
125	35
126	57
127	38

As seen in Table 7, the compounds of the invention have a significant effect on this *in vivo* inflammation model.

[0426]

By using the compounds shown above in Table 7, the following tests (Test Examples 3 and 4) were conducted.

[0427]

Test Example 3: Inhibitory effect on IL-4 stimulated STAT6 phosphorylation

1. Preparation of test compound

The test compound was dissolved in dimethyl sulfoxide (DMSO) to 10 mM, and further diluted with DMSO to the concentrations of 300 and 100 μM. The solution was further diluted with RPMI 1640 medium to 100-fold to obtain a sample solution. Also, DMSO was diluted to 100-fold with RPMI 1640 medium and was used as a negative control.

[0428]

2. Phosphorylated STAT6 activity

The sample solution or the negative control solution (50 μL) was mixed with a solution of DND39 cell (400 μL) (Cell number: 10^5 cells) and shaken at 37 °C for 30 min. 50 μL of Interleukin-4 (10 ng/mL) was added as a stimulant, and the mixture was shaken for 15 min. 500 μL of Fixation buffer (BD Biosciences, Inc.) was added to the mixture, and the mixture was shaken for 10 min to stop the reaction. After centrifuge and removing the supernatant, 500 μL of a membrane permeabilizing agent Perm buffer III (BD

Biosciences, Inc.) was added to the pellet, and was incubated at 4 °C for 30 min. After washing twice with a stain buffer (BD Biosciences, Inc.), Alexa Fluor 647 Mouse Anti-Stat6 (pY641) (BD Biosciences, Inc.) was added, and incubated in a cool dark place for 30 min. The obtained cell solution was subjected to a flow cytometer. The inhibition activity of the test compound was calculated, assuming the GEOMEAN value of the interleukin-4 stimulated negative control group fluorescence intensity as the inhibitory ratio of 0 % and the GEOMEAN value of the non-stimulated negative control group fluorescence intensity as the inhibitory ratio of 100 %. From the results, it was confirmed that the test compounds suppressed IL-4 signaling.

[0429]

Test Example 4: Inhibitory effect on IL-7 stimulated STAT5 phosphorylation

1. Preparation of test compound

The test compound was dissolved in dimethyl sulfoxide (DMSO) to 10 mM and further diluted with RPMI 1640 medium to 100-fold to prepare a sample solution. Also, DMSO was diluted with RPMI 1640 medium to 100-fold was used as a negative control.

[0430]

2. Phosphorylated STAT5 activity

To 100 μL of human fresh blood was added 10 μL of the sample solution or the negative control solution, and shaken at 37 °C for 30 min. 10 μL of interleukin-7 (100 ng/mL) was added as a stimulant, and the mixture was shaken for 15 min. 1.4 mL of Lyse/fix buffer (BD Biosciences, Inc.), which was diluted to 5-fold by distilled water, was added to the reaction system. The mixture was shaken for 10 min, and centrifuged to separate cells. After removing the supernatant, 1 mL of PBS was added to the pellet. After centrifuged to remove PBS, 500 μL of Perm buffer III (BD Biosciences, Inc.) was added, and was incubated at 4 °C for 30 min. After washing twice with Stain buffer (BD Biosciences, Inc.), Alexa Fluor 647 Mouse Anti-Stat5 antibody (pY694) (BD Biosciences, Inc.) was added, and incubated at cool dark place for 30 min. The obtained cell solution was subjected to a flow cytometer. The inhibition activity of the test compound was calculated, assuming the GEOMEAN value of the IL-7 stimulated negative control group fluorescence intensity as the inhibitory ratio of 0 % and the GEOMEAN value of the non-stimulated negative control group fluorescence intensity as the inhibitory ratio of 100 %. From the result, it was confirmed that the test compounds suppressed IL-7 signaling.

[0431]

As shown in Test Examples 1 to 4, the compound of the

invention showed JAK1 inhibitory activity, and thus, is effective in *in vivo* inflammation model.

[0432]

Formulation Example 1

Tablet (oral tablet)

In an 80 mg tablet of the formulation:

Compound of Example 1	5.0mg
Corn starch	46.6mg
Crystalline cellulose	24.0mg
Methylcellulose	4.0mg
Magnesium stearate	0.4mg

According to a conventional method, a mixed powder of the components was tableted to form an oral tablet.

Industrial Applicability

[0433]

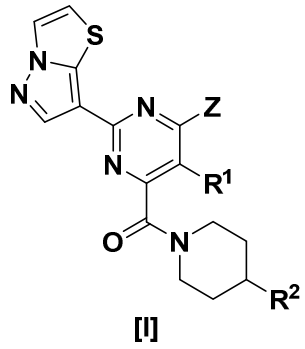
In view of the fact that the compound of the invention or a pharmaceutically acceptable salt thereof exhibits JAK1 inhibitory activity, it is useful as a therapeutic agent for an autoimmune disease (e.g., rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, Castleman's disease, systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, inflammatory bowel disease, Behçet's disease, myasthenia gravis, type 1 diabetes mellitus,

immunoglobulin nephropathy, autoimmune thyroid diseases, psoriasis, scleroderma, lupus nephritis, dry eye, vasculitis (e.g., Takayasu's arteritis, giant cell arteritis, microscopic polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis), dermatomyositis, polymyositis and neuromyelitis optica)), inflammatory diseases (e.g., atopic dermatitis, contact dermatitis, eczema, pruritus, food allergies, bronchial asthma, eosinophilic pneumonia, chronic obstructive pulmonary disease, allergic rhinitis, chronic sinusitis, eosinophilic sinusitis, nasal polyp, allergic conjunctivitis, osteoarthritis, ankylosing spondylitis, Kawasaki disease, Buerger's disease, polyarteritis nodosa and IgA vasculitis), proliferative diseases (e.g., solid cancers, blood cancers, lymph malignant tumor, myeloproliferative diseases, multiple myeloma, pulmonary fibrosis and eosinophilia), sudden hearing loss, diabetic nephropathy, alopecia areata, bone marrow transplant rejection or organ transplant rejection.

CLAIMS

1. A pyrazolothiazole compound represented by the formula [I]:

[Formula 1]



[I]

wherein,

R^1 is hydrogen, alkyl or alkoxy;

Z is $-OR^3$ or $-NR^4R^5$;

in which

R^3 is alkyl, alkyl substituted with cycloalkyl, cycloalkyl, aryl or heteroaryl,

R^4 is hydrogen or alkyl;

R^5 is alkyl, cycloalkyl or saturated heterocyclic group, said alkyl and cycloalkyl in R^5 is optionally substituted with one or two groups selected from the group consisting of the following (1) to (6):

(1) hydroxy,

(2) alkoxy, and difluoroalkoxy,

(3) cycloalkyl, cycloalkyl substituted with (difluoroalkoxy)alkyl, and cycloalkyl substituted with alkoxyalkyl,

(4) saturated heterocyclic group optionally substituted with (difluoroalkoxy)alkyl, (5) aryl, aryl

substituted with halogen, and aryl substituted with alkoxy, and

(6) nitrile, and

said saturated heterocyclic group in R^5 is optionally substituted with one or two groups selected from the group consisting of the following (1) to (3):

(1) alkyl,

(2) alkylcarbonyl, and

(3) alkoxycarbonyl;

R^2 is hydroxy or $-NHR^8$,

in which

R^8 is heteroaryl, heteroaryl substituted with halogen, heteroaryl substituted with alkyl, $-COL^1$, $-COOL^2$ or $-SO_2L^3$,

said L^1 is a group selected from the group consisting of the following (1) to (5):

(1) alkyl, monohaloalkyl, dihaloalkyl, trihaloalkyl, and alkyl substituted with alkoxy,

(2) cycloalkyl,

(3) aryl,

(4) heteroaryl, and

(5) dialkylamino, and cycloalkylamino,

said L^2 is a group selected from the group consisting of the following (1) to (3):

(1) alkyl, monohaloalkyl, dihaloalkyl, trihaloalkyl, and alkyl substituted with alkoxy,

(2) cycloalkyl, and

(3) dialkylaminoalkyl, and

said L^3 is alkyl or cycloalkyl,

or a pharmaceutically acceptable salt thereof, or a solvate

thereof.

2. The pyrazolothiazole compound according to claim 1 or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein R^1 is hydrogen.

3. The pyrazolothiazole compound according to claim 2 or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein

Z is $-NR^4R^5$;

in which

R^4 is hydrogen,

R^5 is alkyl or cycloalkyl,

said alkyl and cycloalkyl in R^5 are optionally substituted with a group selected from the group consisting of the following (1) to (3):

(1) hydroxy,

(2) alkoxy, and

(3) cycloalkyl,

R^2 is hydroxy or $-NHR^8$,

R^8 is heteroaryl, heteroaryl substituted with halogen, heteroaryl substituted with alkyl, $-COL^1$ or $-COOL^2$,

said L^1 is a group selected from the group consisting of the following (1) to (4):

(1) alkyl, monohaloalkyl, dihaloalkyl, trihaloalkyl, and alkyl substituted with alkoxy,

(2) cycloalkyl,

(3) aryl, and

(4) heteroaryl, and

said L^2 is alkyl, monohaloalkyl, dihaloalkyl, trihaloalkyl, alkyl substituted with alkoxy or cycloalkyl.

4. The pyrazolothiazole compound according to claim

3 or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein

R^5 is alkyl, alkyl substituted with hydroxy, alkyl substituted with cyclopropyl or alkyl substituted with alkoxy, and

R^2 is $-NHR^8$.

5. The pyrazolothiazole compound according to claim 3 or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein

R^5 is alkyl having 2 to 6 carbon atoms or alkyl substituted with cyclopropyl,

R^2 is $-NHR^8$,

R^8 is $-COL^1$ or $-COOL^2$,

said L^1 is alkyl having 2 to 6 carbon atoms or cyclopropyl, and

said L^2 is alkyl or cyclopropyl.

6. The pyrazolothiazole compound according to claim 1 which is any one of the following (1) to (135):

(1) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(2) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(3) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(4) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(5) N-(1-{[6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(6) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(7) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(8) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclopropyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(9) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclobutyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(10) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclopentyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(11) N-[1-({6-[({4-[(difluoromethoxy)methyl]tetrahydro-2H-pyran-4-yl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(12) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(13) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b] [1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(14) N-(1-{[6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(15) N-[1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(16) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(17) N-(1-{[6-{[(2S)-1-(difluoromethoxy)propan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(18) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2,2-difluoroacetamide,

(19) N-(1-{[6-{[(1S,2S)-2-methoxycyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(20) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(21) 1-fluoro-2-methylpropan-2-yl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(22) methyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(23) [6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(24) methyl (1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}

piperidin-4-yl)carbamate,

(25) methyl (1-{[6-{[(2S)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(26) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(27) ethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(28) propan-2-yl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(29) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide,

(30) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)pyridine-3-carboxamide,

(31) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)thiophene-2-carboxamide,

(32) N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(33) 1-cyclopropyl-3-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)urea,

(34) [6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyrimidin-2-ylamino)piperidin-1-yl]methanone,

(35) N-(1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(36) N-[1-({6-[(1-methylcyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(37) N-[1-({6-[(1-methoxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(38) methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}
piperidin-4-yl)carbamate,

(39) ethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(40) propan-2-yl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(41) N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}
piperidin-4-yl)benzamide,

(42) N-(1-{[6-(cyclopropylmethoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(43) N-[1-({6-[(3,3-dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(44) N-(1-{[6-(cyclobutyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(45) N-(1-{[6-(cyclopentyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(46) N-(1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(47) N-[1-({6-[(1-hydroxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(48) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,2-oxazol-3-ylamino)piperidin-1-yl]methanone,

(49) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone,

(50) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-methyl-1,2-oxazol-5-yl)amino]piperidin-1-yl}methanone,

(51) N-(1-{[6-{[(2S)-1-hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(52) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(53) methyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(54) propan-2-yl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(55) methyl [1-({6-[(1-hydroxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(56) [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(57) methyl (1-{[6-{[(2S)-1-hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(58) methyl [1-({6-[(3,3-dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(59) methyl (1-{[6-(cyclobutyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(60) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)methanesulfonamide,

(61) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanesulfonamide,

(62) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)ethanesulfonamide,

(63) N-(1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methylpropanamide,

(64) N-(1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2,2-difluoroacetamide,

(65) ethyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(66) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyridin-2-ylamino)piperidin-1-yl]methanone,

(67) ethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(68) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone,

(69) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyrimidin-2-ylamino)piperidin-1-yl]methanone,

(70) methyl [1-({6-[(2-methylbutan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(71) (4-hydroxypiperidin-1-yl)[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]methanone,

(72) propyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(73) propyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(74) propyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(75) propyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(76) propyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(77) methyl [1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(78) 2-methoxyethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(79) 2-methoxyethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(80) 2-methoxyethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(81) 2-methoxyethyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(82) N-(1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide,

(83) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide,

(84) methyl [1-({6-[{[1-(methoxymethyl)cyclopropyl]methyl}(methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(85) 2,2-difluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(86) 2,2-difluoroethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(87) 2,2-difluoroethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(88) 2,2-difluoroethyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(89) tert-butyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(90) 2-methoxyethyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(91) 2-(dimethylamino)ethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(92) 2,2,2-trifluoroethyl (1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(93) 2,2,2-trifluoroethyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(94) 2-methoxy-N-(1-{[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(95) N-(1-{[6-(2-ethylbutoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(96) methyl (1-{[6-(pentan-3-yloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(97) methyl (1-{[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(98) N-[1-({6-[(2-ethylbutyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(99) N-(1-{[6-(pentan-3-yloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(100) methyl [1-({6-[methyl(pentan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(101) methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl](methyl)amino}-2-(pyrazolo[5,1-b] [1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(102) N-(1-{[6-(2-ethylbutoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide,

(103) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl](methyl)amino}-2-(pyrazolo[5,1-b] [1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide,

(104) N-[1-({6-[methyl(pentan-3-yl)amino]-2-(pyrazolo[5,1-b] [1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(105) [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(3-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone,

(106) N-[1-({6-[(2-methoxy-2-methylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(107) (4-hydroxypiperidin-1-yl){6-[methyl(pentan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}methanone,

(108) N-(1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)propanamide,

(109) N-(1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(110) N-(1-{[6-{[(2S)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(111) N-(1-{[6-(pentan-3-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(112) methyl [1-({6-[(2S)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(113) methyl [1-({6-[(2R)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(114) N-[1-({6-[(1-methylcyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(115) [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]{4-[(5-fluoropyridin-2-yl)amino]piperidin-1-yl}methanone,

(116) 2-methyl-N-[1-({6-[(2-methylbutan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(117) N-[1-({6-[(2S)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(118) methyl [1-({6-[tert-butyl(methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(119) cyclopropyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(120) cyclopropyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(121) 2,2-difluoro-N-(1-{[6-{[(2R)-3-methylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)acetamide,

(122) 3-[1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]-1,1-dimethylurea,

(123) 3-(1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-1,1-dimethylurea,

(124) propan-2-yl [1-({6-[(3-methyloxetan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(125) methyl [1-({6-[(dicyclopropylmethyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(126) methyl (1-{[6-phenoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(127) tert-butyl 4-{[6-({4-[(methoxycarbonyl)amino]piperidin-1-yl}carbonyl)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]amino}piperidine-1-carboxylate,

(128) methyl (1-{[6-(piperidin-4-ylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(129) methyl [1-({6-[(1-cyanocyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(130) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(131) methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(132) methyl [1-({6-[(2S)-butan-2-ylamino]-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(133) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(134) methyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate, and

(135) methyl (1-{[2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-(pyridin-3-yloxy)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

7. The pyrazolothiazole compound according to claim 1 which is any one of the following (1) to (58):

(1) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(2) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(3) N-(1-{[6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(4) N-(1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(5) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclopropyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(6) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclobutyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(7) N-[1-({6-[({1-[(difluoromethoxy)methyl]cyclopentyl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(8) N-[1-({6-[({4-[(difluoromethoxy)methyl]tetrahydro-2H-pyran-4-yl}methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(9) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-methyl-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(10) N-(1-{[6-{[(1S,2S)-2-(difluoromethoxy)cyclopentyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(11) N-[1-({6-[(2,2-dimethylpropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(12) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(13) N-(1-{[6-{[(2S)-1-(difluoromethoxy)propan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(14) methyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(15) ethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(16) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)benzamide,

(17) N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(18) propan-2-yl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(19) N-(1-{[6-(cyclopropylmethoxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(20) N-[1-({6-[(3,3-dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(21) N-(1-{[6-(cyclobutyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(22) N-[1-({6-[(1-hydroxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(23) [6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(1,3-thiazol-2-ylamino)piperidin-1-yl]methanone,

(24) N-(1-{[6-{[(2S)-1-hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(25) methyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(26) propan-2-yl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(27) methyl [1-({6-[(1-hydroxy-2-methylpropan-2-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(28) [6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl](4-hydroxypiperidin-1-yl)methanone,

(29) methyl (1-{[6-{[(2S)-1-hydroxy-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(30) methyl [1-({6-[(3,3-dimethylbutan-2-yl)oxy]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(31) methyl (1-{[6-(cyclobutyloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(32) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanesulfonamide,

(33) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)ethanesulfonamide,

(34) ethyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(35) [6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl][4-(pyridin-2-ylamino)piperidin-1-yl]methanone,

(36) propyl (1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(37) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)-2-methoxyacetamide,

(38) 2,2-difluoroethyl (1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(39) 2,2-difluoroethyl (1-{[6-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(40) tert-butyl (1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(41) 2-methoxyethyl(1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(42) 2-(dimethylamino)ethyl(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(43) 2,2,2-trifluoroethyl(1-{[6-{[(1R)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(44) 2,2,2-trifluoroethyl(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(45) methyl(1-{[6-(pentan-3-yloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(46) N-[1-({6-[(2-ethylbutyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]cyclopropanecarboxamide,

(47) N-(1-{[6-(pentan-3-yloxy)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(48) methyl[1-({6-[(2S)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(49) methyl[1-({6-[(2R)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(50) N-[1-({6-[(1-methylcyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]propanamide,

(51) methyl[1-({6-[tert-butyl(methyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(52) cyclopropyl(1-{[6-(tert-butylamino)-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(53) propan-2-yl[1-({6-[(3-methyloxetan-3-yl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(54) methyl[1-({6-[(1-cyanocyclopropyl)amino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(55) methyl[1-({6-[(2S)-butan-2-ylamino]-5-methoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,

(56) methyl(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(57) methyl(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-5-ethoxy-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate, and

(58) methyl(1-{[2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)-6-(pyridin-3-yloxy)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

or a pharmaceutically acceptable salt thereof, or a solvate thereof.

8. The pyrazolothiazole compound according to claim 1 which is any one of the following (1) to (8):

(1) N-(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(2) N-(1-{[6-{[(2R)-3,3-dimethylbutan-2-yl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(3) methyl(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(4) ethyl(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(5) N-(1-{[6-{[(1S)-1-cyclopropylethyl](methyl)amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)cyclopropanecarboxamide,

(6) propan-2-yl(1-{[6-{[(1S)-1-cyclopropylethyl]amino}-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl]carbonyl}piperidin-4-yl)carbamate,

(7) methyl[1-({6-[(2S)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate, and

(8) methyl[1-({6-[(2R)-butan-2-ylamino]-2-(pyrazolo[5,1-b][1,3]thiazol-7-yl)pyrimidin-4-yl}carbonyl)piperidin-4-yl]carbamate,
or a pharmaceutically acceptable salt thereof, or a solvate thereof.

9. A pharmaceutical composition comprising the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 as an active ingredient.

10. The pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 for use as a JAK1 inhibitor.

11. Use of the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 in the manufacture of a medicament, wherein the medicament is a JAK1 inhibitor.

12. The pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 for use as a therapeutic agent for an inflammatory disease.

13. The pyrazolothiazole compound for use according to claim 12 wherein the inflammatory disease is atopic dermatitis, eczema, bronchial asthma, eosinophilic pneumonia, chronic obstructive pulmonary disease, allergic rhinitis, eosinophilic sinusitis, nasal polyp, ankylosing spondylitis or eosinophilic esophagitis.

14. Use of the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 in the manufacture of a medicament for therapeutic treatment of an inflammatory disease.

15. The use according to claim 14 wherein the inflammatory disease is atopic dermatitis, eczema, bronchial asthma, eosinophilic pneumonia, chronic obstructive pulmonary disease, allergic rhinitis, eosinophilic sinusitis, nasal polyp, ankylosing spondylitis or eosinophilic esophagitis.

16. The pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 for use in the treatment of an autoimmune disease.

17. The pyrazolothiazole compound for use according to claim 16 wherein the autoimmune disease is rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, Castleman’s disease, systemic lupus erythematosus, Sjögren’s syndrome, inflammatory bowel disease, psoriasis, scleroderma, dry eye, Takayasu’s arteritis, giant cell arteritis, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis or neuromyelitis optica.

18. Use of the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment of an autoimmune disease.

19. The use according to claim 18 wherein the autoimmune disease is rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, Castleman's disease, systemic lupus erythematosus, Sjögren's syndrome, inflammatory bowel disease, psoriasis, scleroderma, dry eye, Takayasu's arteritis, giant cell arteritis, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis or neuromyelitis optica.

20. The pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 for use as a therapeutic agent for a proliferative disease.

21. The pyrazolothiazole compound for use according to claim 20 wherein the proliferative disease is solid cancers, blood cancers, lymph malignant tumor, myeloproliferative diseases, multiple myeloma, pulmonary fibrosis or eosinophilia.

22. Use of the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 in the manufacture of a medicament for therapeutic treatment of a proliferative disease.

23. The use according to claim 22 wherein the proliferative disease is solid cancers, blood cancers, lymph malignant tumor, myeloproliferative diseases, multiple myeloma, pulmonary fibrosis or eosinophilia.

24. The pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 for use in the treatment of diabetic nephropathy, alopecia areata, bone marrow transplant rejection or organ transplant rejection.

25. Use of the pyrazolothiazole compound or a pharmaceutically acceptable salt thereof or a solvate thereof according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment of diabetic nephropathy, alopecia areata, bone marrow transplant rejection or organ transplant rejection.